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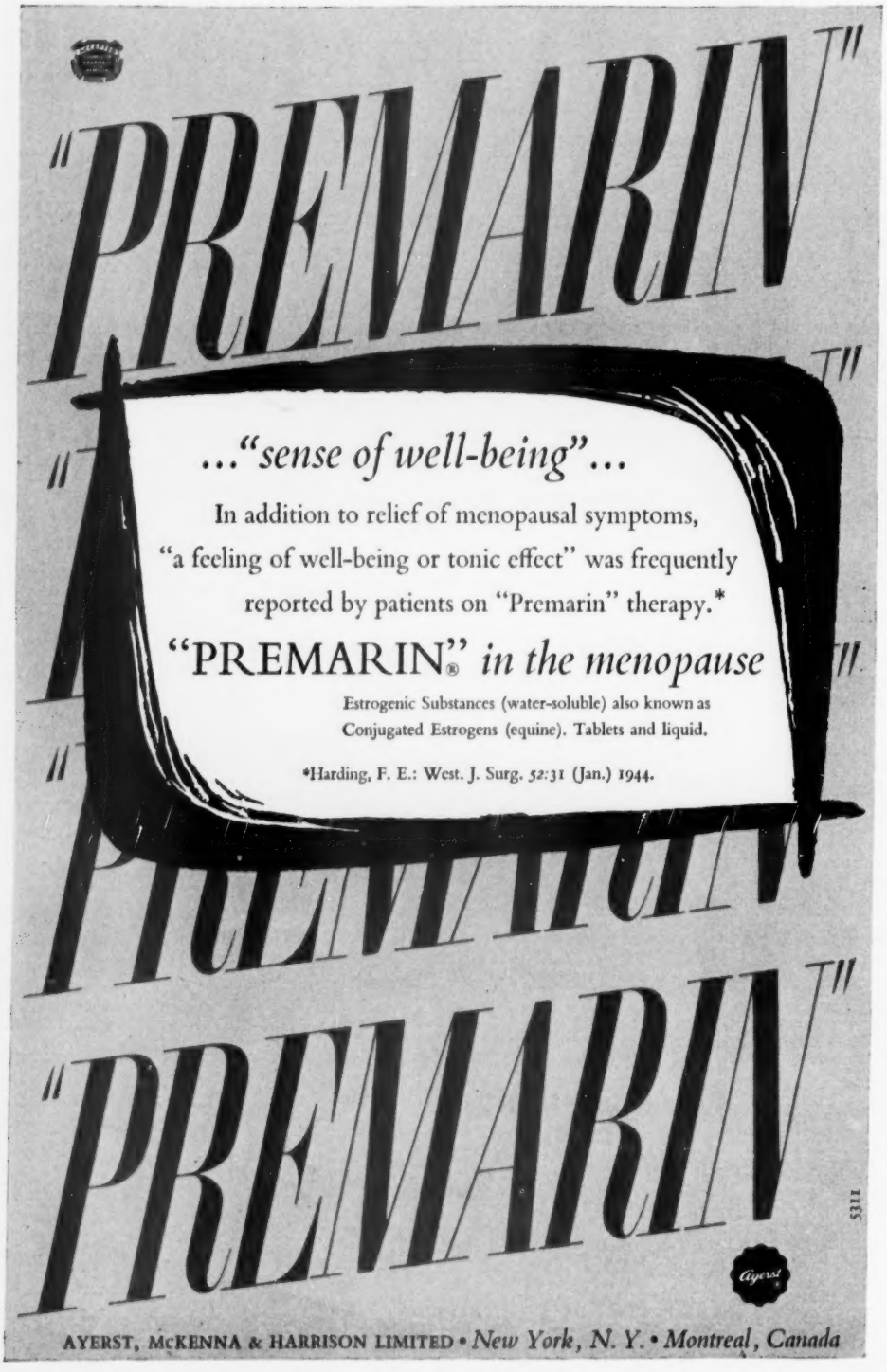
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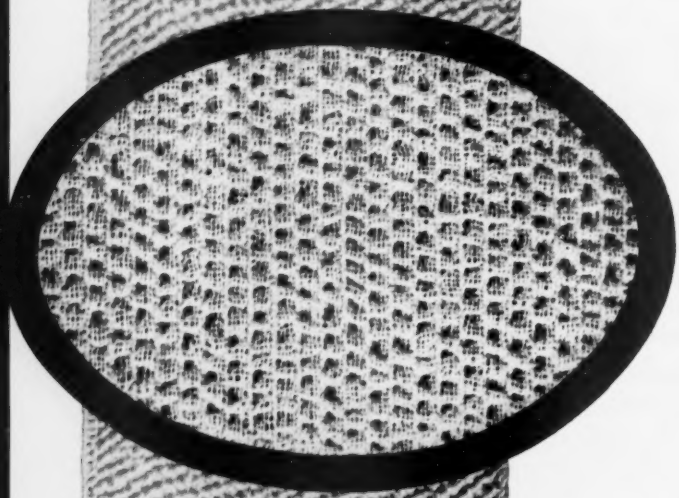

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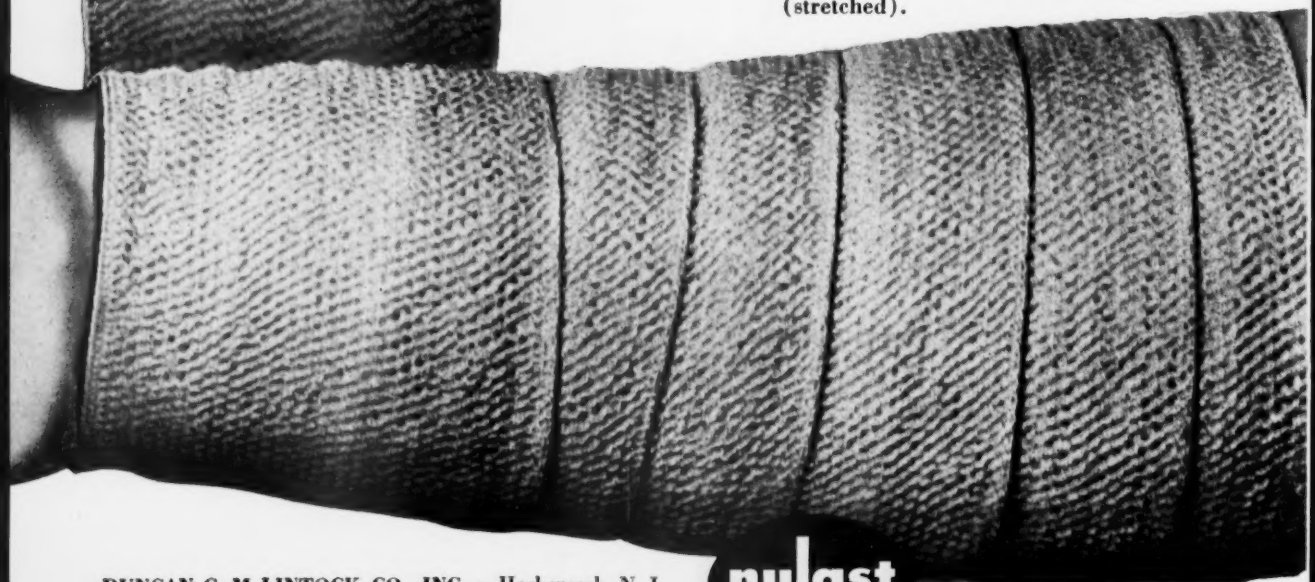

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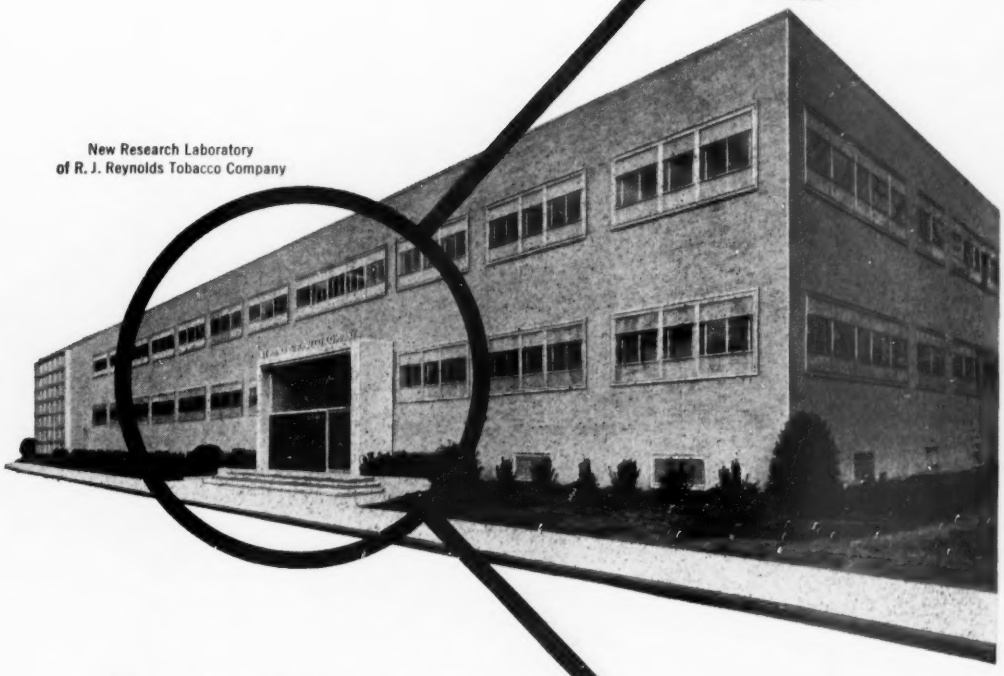

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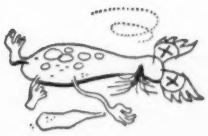

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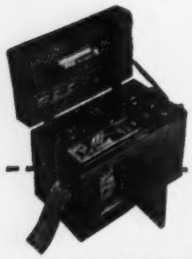

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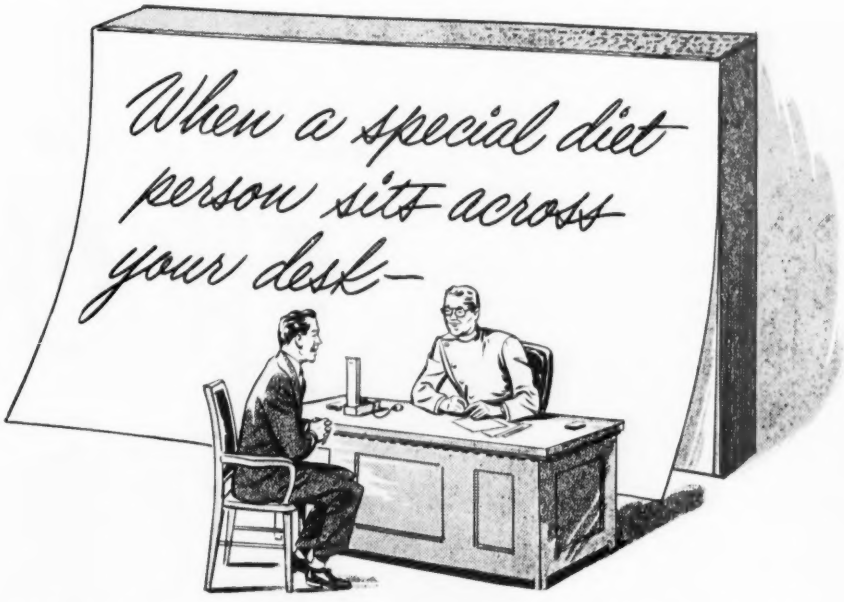

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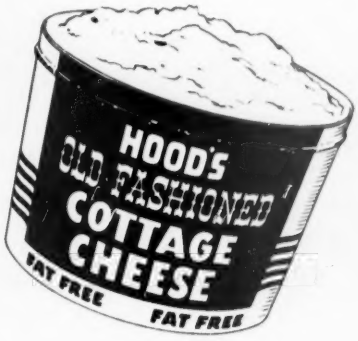

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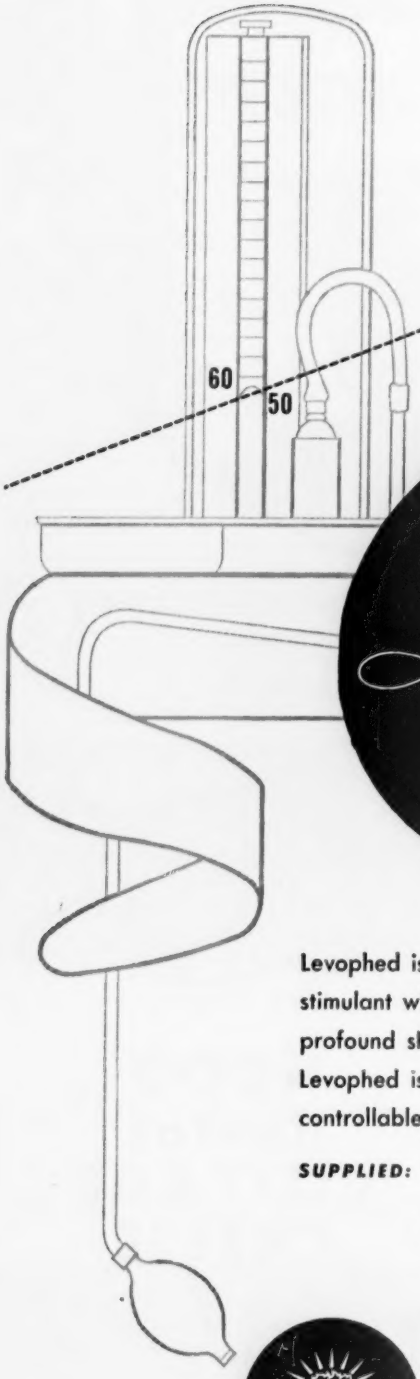

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Volume 249 JULY 16, 1953 Number 3

THE MANAGEMENT OF ESSENTIAL HYPERTENSION*

GARFIELD G. DUNCAN, M. D.,† AND ROBERT J. GILL, M. D.‡

PHILADELPHIA

THE prevalence of essential hypertension, its crippling potentialities and its threat to life make it one of the greatest of clinical problems. The complexities are all the greater because a combination of influences, rather than a single factor, produces the phenomenon. Adrenocortical function and its influence on sodium metabolism and renal function, the kidneys and the secondary part that they play in retaining sodium in this disease, the pressor substances elaborated in the kidneys and elsewhere and the effect that central stimulation exerts on these processes are among the considerations in its management. It is not surprising in view of these multiple influences, that numerous therapeutic agents, each exerting favorable effects in some but not all cases, are employed in the control of essential hypertension.

OUTLOOK AND CLINICAL EVALUATION

Despite the enigma of essential hypertension, it is possible to select a treatment or a combination of treatments that, when wisely applied, offer hope to patients in whom the disease has not reached the stage of advanced renal decompensation.

The cardiovascular-renal evaluation when the patient is first seen may reveal gradations from the mildest to the most grave forms of essential hypertension. Also, basic information with which to compare subsequent findings is established. With the results of a cardiovascular-renal survey at hand, progression of the hypertensive disorder may be identified earlier than would otherwise be possible and appropriate measures may be taken before the prognostic signs make them inadvisable—for example, the life-saving potential of a sympathectomy in the properly selected case may be sacrificed if the underlying disorder has been allowed to progress to the state of renal decompensation.

Essential hypertension permits, for most patients, a reasonably good longevity, as stressed by Ranges[1] and by O'Hare and Holden,[2] but the prognosis is unfavorable with severe grades of the disease as indicated in Hamman's[3] study, which revealed a mortality of 78 per cent in a ten-year period. Fortunately, it is possible, despite much loose writing to the contrary, to predict with reasonable accuracy which patient will continue with a benign hypertension and which will be the victim of serious progression of the disease. Such predictions, accurately arrived at, will prevent many patients with benign hypertension from being subjected, needlessly, to surgical measures. Results of surgical therapy compared with those of nonsurgical measures are usually misleading. The comparison, for the most part, is between the results of surgery and those from no treatment or from medical treatment far short of the optimum. Probably not more than 6 per cent of hypertensive patients should be subjected to sympathectomy. We wish to make it clear that we are ardent supporters of the procedure when the patient presents the criteria for and qualifies as a not too unfavorable risk for this procedure. We have simplified the detection and study of patients for whom we think sympathectomy is the procedure of choice.

Appropriate studies should exclude diseases other than essential hypertension that might account for the elevated blood pressure. Notable among these are coarctation of the aorta, pheochromocytoma, periarteritis nodosa, Cushing's syndrome, thyrotoxicosis, chronic glomerular nephritis, pyelonephritis, disseminated lupus erythematosus, unilateral renal disease and multiple myeloma.

A classification of essential hypertension based solely on the blood-pressure readings will include a great element of error. The blood pressure is not the sole or even the chief criterion of the degree of hypertensive disease. If a patient is under observation for a sufficient period it is ordinarily a simple matter to evaluate, first, the grade of severity of the resting blood-pressure readings, secondly, the degree of arterial changes by study of the peripheral arteries, ocular fundi and heart, including the electrocardiograms and the ballistocardiogram, which appears to be of more importance than the electrocardiogram, and, thirdly, the degree of renal involvement by determination of protein and cellular content of the urine, the ability to dilute and con-

*Presented at a meeting of the Boston City Hospital House Officers' Association, Boston, January 22, 1953.

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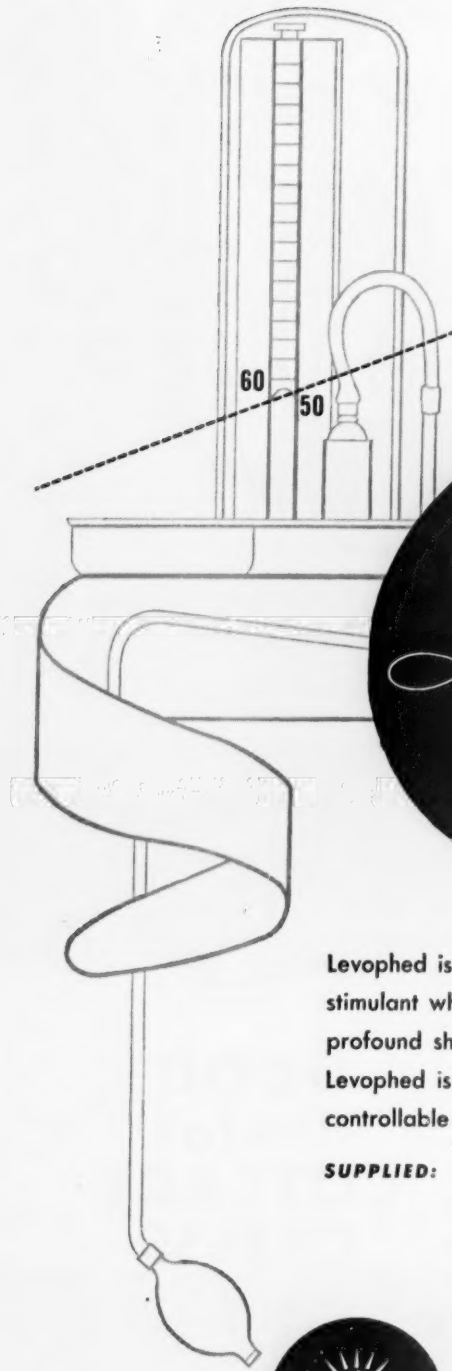

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centrate the urine, the concentration of urea in the blood, excretory pyelograms and phenolsulfonephthalein excretion tests.

These studies have the added advantage of providing a basis with which to compare subsequent findings. This is especially important since it gives evidence against the necessity for surgery when minor changes only are recorded on subsequent evaluations. On the other hand, the detection of patients who, despite treatment, show progressive disease may permit surgery when greatest benefit is likely to be gained from it.

Choice of Therapy

Medical measures—general and special—suffice for most patients with essential hypertension. A "sodium-depletion" regimen is of great value, but it has its limitations and must be supplemented with drug therapy in a good many cases and by surgery in a few.

Our objective in this paper is to correlate the respective grades of hypertensive disease with the therapies that, in our experience, promise optimum results. These therapies are summarized as follows:

Outline of Therapy According to the Degree of the Hypertensive Processes

I. Mild degrees of hypertensive disease with intermittent, or sustained, elevation of the blood pressure.
   (a) Reduce weight if indicated.
   (b) A plan aimed at achieving tranquillity.
      1. Eliminate emotional conflicts.
      2. Achieve adequate rest with prevention of excessive responsibilities.
      3. Avoid excesses — notably overwork and excessive intake of salt.

II. Moderate to severe degrees of hypertensive disease with a sustained hypertension—for example, systolic pressures of 170-230 and diastolic pressures of 105-120 and patients for whom measures outlined in I have failed.
   (a) Applicable features of I, plus
   (b) Sodium depletion
      1. Sodium intake 200 mg. or less per day if dietary restriction of sodium is being relied upon alone, and if necessary
      2. Exchange resin therapy: Resodec 15 gm. three times a day or Carbo-Resin 16 mg. three times a day and, if necessary
      3. Hypotensive drugs: *Rauwolfia serpentina*, veratrum or hydrazinophthalazine (Apresoline), or hexamethonium chloride or Dibenzyline.

III. Severe hypertensive disease with evidence of unfavorable progression — for example, blood pressures of 220-280 systolic and 120-140, or more, diastolic after therapy has proved inadequate.
   (a) Therapy II is given a trial and if inadequate,
   (b) Sympathectomy if candidate qualifies (see text).
   (c) Applicable features of I.

IV. Diastolic pressure remains above 100 after sympathectomy.
   (a) Sodium restriction to 1.0 gm. if tolerated (2 gm. of sodium may be necessary to prevent low-salt syndrome) and, if necessary.
   (b) Exchange-resin therapy, and, if necessary
   (c) Hypotensive drugs.
   (d) Applicable features of I.

V. Sustained severe hypertension (diastolic pressure above 130) and without azotemia if measures outlined in IV have failed, and if vascular disease appears to be progressing unfavorably.
   (a) Adrenalectomy, and, if necessary
   (b) Regulation of sodium intake, and, if necessary
   (c) Substitution therapy — cortisone and DOCA

VI. Malignant hypertension with azotemia
   (a) High-fat, high-carbohydrate, low-protein (20 gm.) diet.
   (b) Sedation.
   (c) Pyrogen therapy — if renal decompensation has not gone too far.
   (d) Occasionally methonium will reverse the malignant phase but usually it is of no help and may be actually harmful especially if renal failure has supervened.

General Measures

The adoption of appropriate general measures, notably a reduction of obesity and the avoidance of excesses of salt in the diet and reduction of undue anxiety with the administration of mild sedatives such as phenobarbital will aid in correcting and controlling essential hypertension in its early phases. It is not known how many patients with hypertension are effectively treated by these simple measures, but surely the number is great.

Sodium Depletion

For the next grade of severity of hypertension—in which the hypertension is sustained and does not respond adequately to general measures and yet the more radical measures are not indicated—a more intensive salt depletion, as advocated by Allen,[4] is effective. The restriction of the sodium intake should be sufficient to achieve a reduction of the sodium excretion in the urine to 0.5 gm. or less in twenty-four hours—a difficult matter by dietary restriction

alone. However, the sodium depletion may be enhanced appreciably by the use of exchange resins.[5] Our experience has been largely with Resodec,* a cation-exchange resin, and Carbo-Resin,† a mixed cation and anion resin. Between 1 and 3 gm. of sodium, the amounts depending upon the intake of sodium, is carried off via the gastrointestinal tract by these resins adminstered in doses of 15 gm. three times daily. Symptoms from sodium deprivation are unusual in hypertensive patients who have a greater than normal ability to retain sodium.

TABLE 1. *Effect of Resin Therapy on Urinary Sodium and Diastolic Pressure.**

URINE SODIUM EXCRETION	MEAN REDUCTION IN DIASTOLIC PRESSURE	
	20 OR MORE	BOTH 20 OR MORE AND TO 100 OR LESS
gm./24 hr.	*no. of patients*	*no. of patients*
0.5 or less	15	11
0.5–0.9	5	4
1.0 or more	3	1
Totals	23	16

*In a series of 54 patients the hypotensive effects of sodium depletion are most pronounced when the sodium excreted in the urine is less than 0.5 gm. per 24 hours; the greater the amount of sodium in the urine, the less the hypotensive effect.[5]

The relation between the degree of salt depletion and the reduction in the blood pressure is shown in Table 1, and the increased sensitivity of the sympathectomized patient to salt depletion is illustrated in Table 2.

It will be observed that in L. T. (Table 2) the mean of postsympathectomy blood-pressure readings, over a period of six months, was 194 systolic, 132 diastolic. This is compared with a subsequent mean pressure of 138 systolic, 90 diastolic, over a period of fourteen months when sodium depletion was intensified by resin therapy. Also, R. F. (Table 2) had a mean of 190 systolic, 130 diastolic, for seven months after sympathectomy. In contrast is the mean reading of 128 systolic, 95 diastolic, covering a period of a year during which resin therapy was added.

F. D. (Table 2), who had more advanced hypertensive disease, had a mean blood pressure of 160 systolic, 120 diastolic, for three months after sympathectomy. Neither resin therapy nor Apresoline singly controlled the blood pressure, but when these forms of treatment were combined a mean pressure of 140 systolic, 100 diastolic, was achieved.

The exchange-resin method of depriving the organism of sodium, although highly effective, is not a substitute for restriction in dietary sodium. It permits a more palatable diet, however, and hence one that is more likely to be observed. Too strict sodium depletion is contraindicated in the presence of azotemia. Resins may be used only when renal function is at least moderately good.

The rice diet of Kempner[6] appears to carry no advantage for the hypertensive patient that is not to be had in other diets low in sodium content.[7] The low-protein content of the rice diet has a beneficial effect in uremic states, in which the high-calorie, low-protein diet of Kolff[8] is preferred.

Hypotensive Drugs

With the exception of their use in dealing with hypertensive crises, these drugs are recommended only after the foregoing measures have been in-effective and in cases not considered suitable for sympathectomy. This group of patients probably comprises over half the number with severe hypertension. We prefer also to use the hypotensive drugs in addition to, and not in place of, the general measures and sodium depletion already referred to. These measures, by supplementing the effects of the hypotensive drugs, are advantageous when one is dealing with potentially dangerous drugs. None of the hypotensive drugs now available have been in use long enough for a seasoned judgment of their ability to prevent progress of the vascular disease or to prolong life and lessen complications in hypertension.

TABLE 2. *Effect of Resin Therapy after Failure of Sympathectomy.*

PATIENT	SEX	AGE	DURATION OF HYPERTENSION	CHANGES IN FUNDI	SEVERITY OF SYMPTOMS	MEAN BLOOD-PRESSURE READINGS		
						BEFORE SYMPATHECTOMY	AFTER SYMPATHECTOMY	AFTER ADDITION OF RESIN THERAPY
		yr.	*yr.*					
L. T.	F	49	12	Grade 2	+++	240/149	194/132 (6 mo.)	138/90 (14 mo.)
R. F.*	F	41	4	Grade 4	++++	242/148	190/130 (7 mo.)	128/95 (1 yr.)
F. D.*	F	33† 45‡	19	Grade 2	++++	225/150 200/134	160/120 (3 mo.)	140/100 (4 mo.)§

*Patient also had hemiplegia.
†First sympathectomy (9th thoracic to 1st lumbar segment) performed in 1940.
‡Second sympathectomy (2d thoracic to 1st lumbar segment) performed in 1951.
§Apresoline, 150 mg. a day, added. Both resin and Apresoline needed, since neither alone controls this patient's blood pressure.

*Available from Smith, Kline and French Laboratories, Philadelphia.
†Available from Eli Lilly and Company, Indianapolis, Indiana.

Of the hypotensive drugs available, our experience has been for the most part with Veratrum alkaloids,* 1-hydrazinophthalazine (Apresoline), hexamethonium chloride, Dibenzyline† and various combinations.

Veratrum.[9, 10] There is a small margin between the therapeutic dose of veratrum preparations and that which causes toxic effects, notably nausea and vomiting. However, in addition to general measures and sodium depletion, the administration of Veriloid (VPM) may mean the difference between success and failure. The product Veriloid, for intravenous use, is of special value in correcting hypertensive crises, as is hexamethonium administered parenterally. We consider the veratrum product the safer of the two for this purpose. There is little or no tendency on the part of hypertensive patients to develop a tolerance to veratrum preparations, which, when satisfactorily effective, are to be preferred to the more powerful agents—1-hydrazinophthalazine (Apresoline) and hexamethonium chloride. The effects of veratrum therapy, however, are not as predictable as those of the latter two drugs. Dosage schedules for veratrum preparations vary with the product.‡ It is still debatable whether or not protoveratrine is superior to the mixtures of veratrum.

Hyrdazinophthalazine (Apresoline).[9-11] Administered orally, beginning with 10 mg. four times daily after food and increasing gradually to 200 mg. in each dose, this drug may have good results in two to eight weeks. Apresoline reduces the blood pressure, according to Schroeder[11] and Page,[10] by its inhibiting action on pressor agents elaborated by the midbrain. Approximately a third of patients suffer no side effects or minor ones, which subside in another third after two or three weeks of therapy. The unfavorable side effects are headache, edema, palpitation, giddiness, angina, vomiting, general malaise and occasionally a febrile response. Patients with borderline cardiac failure have been thrown into definite failure during Apresoline therapy because of tachycardia and widening of the pulse pressure. Persistent therapy, 200 mg. daily for eight weeks, should be allowed before the drug is considered a failure.

Hexamethonium chloride.[9, 12] This effective ganglion-blocking agent is a powerful hypotensive drug. The initial dose suggested is 10 to 25 mg. subcutaneously with a maintenance dosage of 25 to 100 mg. three times daily. Larger doses are given, if necessary, to obtain the desired result. Hexamethonium therapy has given gratifying results in some cases of relatively refractory malignant hypertension with relatively good renal function still intact. Irregularities of absorption make the oral administration of this drug too dangerous for routine clinical use. Patients may be taught to administer hexamethonium subcutaneously just as diabetic patients administer insulin. Unfavorable side effects are severe postural hypotension, urinary retention and ileus. Deaths have occurred as the result of this therapy. Side effects are more severe in the elderly patients, a circumstance that contraindicates the use of this drug in patients over sixty years of age. It is also contraindicated in the presence of coronary and renal insufficiency. At present this is our last choice among the various depressor drugs because of its powerful and potentially dangerous effects.

Alternate doses of Apresoline and hexamethonium seem to carry less risk than hexamethonium therapy alone, and when used to supplement the sodium depletion therapy, relatively small doses may be effective, although there is not yet general agreement that this combined therapy has any advantage over either drug alone. For instance, the doses may be gradually increased to 100 mg. of Apresoline and 50 to 100 mg. of hexamethonium given alternately at intervals of approximately six hours. The development of a tolerance to both Apresoline and hexamethonium is common and is compensated for by an increase in the amounts given. Constipation must be prevented if risk of serious side effects from hexamethonium is to be avoided. By alternating these two drugs, one reduces the danger of accumulation of hexamethonium in the intestinal tract with the hazard that attends its subsequent absorption. When these drugs are being discontinued, the amounts given should be tapered off gradually to prevent precipitating pulmonary edema. Occasionally, on withdrawal of the drugs in a case of severe hypertension, the progress of the disease seems to be accelerated. This is especially true in malignant hypertension.

Dibenzyline. This adrenergic blocking agent is sometimes an effective agent when given orally.[13] It is advisable to begin with small doses, 10 mg. thrice daily, with subsequent increases until satisfactorily effective results are achieved or the maximum dosage tolerated is reached. The preparation for intravenous use in doses of 0.7 to 1.0 mg. per kilogram of body weight is abruptly effective

*Veriloid (containing all the ester alkaloids of veratrum viride), available from Riker Laboratories, Los Angeles, California; Vertavis and Veratrite available from Irwin Neisler and Company, Decatur, Illinois; Protoveratrine, a single-ester alkaloid of *Veratrum album*.

†Available from Smith, Kline and French Laboratories, Philadelphia.

‡Vertavis contains 30-60 craw units daily. Veratrite — each tabule contains whole powered *Veratrum viride*, sodium nitrate and phenobarbital; dosage 3 to 6 tabules daily. Veriloid — orally 8 to 20 mg. daily (Veriloid-VP contains phenobarbital and Veriloid; Veriloid-VPM contains phenobarbital, mannital hexanitrate and Veriloid). Veriloid — intravenously for hypertensive crises (1 cc. contains 0.4 mg. of Veriloid) 0.15 cc. per 10 pounds of body weight; this amount is diluted in physiologic saline solution to 10 cc., and 4 cc. is injected slowly — 0.5 cc. per minute (after a delay of two minutes the injection is resumed until the desired effect is achieved or until toxic manifestations occur). Protoveratrine — orally 400 to 1500 microgm. daily and intravenously 50 to 150 microgm. (100 microgm. diluted in 10 cc. of physiologic saline solution and injected slowly until the desired effect is obtained or toxic symptoms are manifest).

in reducing blood pressure in hypertensive crises. The action of this drug also seems to be enhanced by the sodium-depletion regimen, and it appears to be quite effective in blocking the sudden large rises in blood pressure that hypertensive patients exhibit with activities and positional changes. Unfavorable side effects are less frequent than those of orally administered hexamethonium. Stuffiness of the nasal passages, dryness of the mouth and constriction of the pupils usually occur to some degree. Symptoms of postural hypotension and tachycardia and, less frequently, nausea, vomiting and headache have complicated this therapy. These effects tend to subside as treatment is continued.

The effects of tetraethyl ammonium (T. E. A. C.), Dibenamine and nitrites are too transitory for these substances to be of value in the routine management of essential hypertension. Thiocyanate has no apparent advantage over the salt-depletion regimen, and there is the danger of thiocyanate toxicity.

Rauwolfia serpentina, alone and in combination with veratrum or Apresoline has been reported to be a modestly effective oral hypotensive agent by Wilkins and Judson.[14] It needs further standardization and study before being made generally available.

Sympathectomy

The patient with a severe degree of hypertensive disease who has diastolic pressures, for the most part, above 130 and whose response to the foregoing measures is not satisfactory—even though he may be free from symptoms, or nearly so—is a possible candidate for sympathectomy. So also is the patient who, under observation and conservative treatment, exhibits relentless progression of the hypertensive disease from the milder to the moderately severe and malignant state in a matter of months. With this information at hand, it has been our custom to pose the question: "Is it reasonably likely, on the basis of clinical experience, that this patient will survive for five years if a sympathectomy is not performed?" If the answer is "Yes" no immediate action is taken, and another evaluation is made a few months later. If the answer is "No" the patient is admitted to the hospital and studied to determine if he qualifies for the operation. Most studies to which these patients are subjected are needless and often misleading. Assuming that the diagnosis of essential hypertension is correct and barring complications that might make surgery untenable, only three criteria are necessary to qualify the patient for the operative procedure: in the first place the patient—with rare exceptions—should not be over fifty-five years of age, and preferably below fifty; secondly, cardiac enlargement, if present, must not exceed normal dimensions by 50 per cent—dimensions to be determined by actual measurement with fluoroscopic aid; and, thirdly, there must be no increase above 24 mg. per 100 cc. in the blood urea nitrogen. If the patient is disqualified by any one or more of these criteria and the disqualification is disregarded and a sympathectomy is proceeded with, the outlook is highly unfavorable.

TABLE 3. *Results of Sympathectomy in Essential Hypertension.**

PATIENT	SEX	AGE	MEAN BLOOD PRESSURE		DURATION OF FOLLOW-UP STUDY	KNOWN DURATION OF HYPERTENSION BEFORE OPERATION	FUNDI BEFORE OPERATION	SEVERITY OF SYMPTOMS BEFORE OPERATION
			BEFORE OPERATION	AFTER OPERATION				
		yr.			yr.	yr.		
E. W.	F	44	180/120	140/80	4¾	2	+	+++
A. J.	M	55	180/115	140/90	4½	24	+++	++++
B. G.	F	42	190/120	125/80	4½	7	++	++
J. E.	M	48	200/120	130/85	1¾	3	+++	+++
V. H.	M	42	200/124	132/87	¾	(?) 20	++	+++
H. W.	M	42	215/134	150/100	2½	1	++	++++
M. D.	F	53 (?)	240/137	150-180/90-100	⅛	1½	++	+

*The clinical improvement was equally good.

Although only 7 of our private patients have been subjected to sympathectomy since 1946, highly favorable results, in suitably selected patients, are indicated in Table 3. The ensuing pressure, in each case, is practically normal without postoperative therapy. Three ward patients with more advanced disease did not get such good responses from sympathectomy (Table 2). However, in 2 of these sodium depletion was effective in attaining satisfactory blood-pressure readings and freedom from

The same surgical technic has been employed for each of our patients—namely, the sympathetic chain on each side, at separate operations, was removed intact from the second or third thoracic to the second lumbar segment. The second lumbar segment is allowed to remain on one side in most male patients. In the event of tachycardia and other evidences of advanced organic cardiac disease, removal up to and including the first thoracic segment is considered a safeguard against subsequent tachycardia and possible acute myocardial failure.

symptoms. The third patient, F. D., required Apresoline, 150 mg. daily, in addition to sodium depletion to achieve a good result.

In R. F., the sensitiveness to sodium depletion after sympathectomy was so great that the salt intake has been unrestricted. This patient prefers taking the resin to observing restrictions in dietary sodium.

Attempts were made to abandon the resin therapy in each of these 3 cases, but on each occasion hypertension promptly ensued.

Adrenalectomy

To date we have had no experience with subtotal or total adrenalectomy, the reason being that no patient has filled the criteria we have set for it—namely, severe hypertension that has not responded sufficiently to the foregoing measures in a patient who has relatively good renal function. Wolferth and his co-workers[15] report that better results follow a subtotal adrenalectomy in patients who previously had been subjected to sympathectomy. Adrenalectomy is still in the research phase, and the prospects are that it may prove to be the treatment of choice in only a small percentage of hypertensive patients.

Pyrogen Therapy

A trial of pyrogen therapy or hexamethonium has a place in the treatment of malignant hypertension with relatively intact renal function.

A regression of malignant changes in hypertensive disease after pyrogen therapy has been observed by Page.[10,16] Fever was produced with a soluble bacterial pyrogen in a 200-cc. saline infusion in amounts sufficient to increase the daily temperature to 101 to 102°F. The renal function must not be excessively low. Therapy is continued for at least six days and prolonged as long as favorable progress continues — usually three or four months. Hexamethonium therapy has given promising results in some of these relatively refractory cases in which renal failure has not yet developed.

Diet Therapy for Malignant Hypertension with Pronounced Azotemia

Kolff[8] has reported favorably on the effects of diets high in calories, 2000 to 3000, and low in protein, 20 gm. daily, in the treatment for chronic uremia. Sodium restriction is contraindicated in this group.

Summary and Conclusion

An outline of therapy for various gradations of essential hypertension is presented with indications for the several measures.

Importance is attached to the evaluation of hypertensive disease as early as possible, the tendency for hypertensive disease to remain in the benign phase in the majority of patients, the benefit from the depletion of sodium in the body by restricted intake and by the use of exchange resins and to the increased sensitivity to the sodium depletion after sympathectomy, the hypotensive drugs, simplified criteria for sympathectomy and for subtotal adrenalectomy, and therapies that combine pharmacologic effects and provide more favorable responses than those gained by a single hypotensive agent.

We are indebted to Dr. Lawrence S. Carey for permission to include the record of one of his patients who was subjected to sympathectomy according to the criteria outlined, to Dr. Edward W. Bixby for his interest in, and interpretations of, the ballistocardiographic studies, and especially to Drs. John B. Flick, Sr., and John B. Flick, Jr., on whom we relied for the surgical procedures described in this study.

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IDIOPATHIC ULCERATIVE COLITIS BEGINNING AFTER THE AGE OF FIFTY*

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THE general concept of idiopathic ulcerative colitis as a disease occurring predominantly in the second and third decades of life must be modified in the light of accumulating evidence that the disorder is seen with significant frequency both in childhood and in the later years of life. It is not a clinical rarity to observe an elderly person with a reactivation of an ulcerative colitis that had its initial onset during the earlier decades. Quite distinct from such patients are those whose symptoms of colitis appeared for the first time after the age of fifty. A careful review of the latter group has been undertaken to draw additional attention to its clinical importance, to the modifications produced by the aging process itself and to the results that can be expected of medical and surgical management. Twenty patients in this classification were seen at the Beth Israel Hospital from 1941 through 1952. Seventeen had not taken aureomycin or terramycin before or during the illness, so that the observations reported are uncomplicated by the potentially adverse effects of such agents on the enteric mucous membrane.[1-4] Three patients who received such antibiotics as therapy after the colitis had become established are also included for comparison.

METHOD

The records of all patients fifty years of age or older with idiopathic ulcerative colitis who were treated at the Beth Israel Hospital from 1941 to 1952 inclusive were reviewed. Records that contained any intimation that the disease had begun before the sixth decade of life were excluded from this study. In addition, to establish this point beyond any reasonable doubt, the records of previous hospital admissions elsewhere were investigated, and the office files of the patient's private physician were consulted. The majority of the 20 patients selected had been seen during their hospitalization by one or both of us. The diagnosis was based on typical sigmoidoscopic findings, characteristic roentgenographic appearance of barium-enema studies and the pathological findings in specimens obtained at operation or post-mortem examination. Stool cultures for enteric pathogens were done routinely unless precluded by emergency surgery, and in 11 cases the stools were also examined for amebas. Nine patients had blood studies for febrile agglutinins, and almost all were given x-ray examinations of the chest. A follow-up evaluation or report was obtained for every patient included in this study, by direct contact with the patient or his family, by communication with other hospitals and by inquiries of the patient's personal physician.

RESULTS

A total of 20 cases are included in this report, representing approximately 10 per cent of all patients with idiopathic ulcerative colitis admitted to the hospital during the years 1941 to 1952 inclusive. This is a somewhat higher proportion of cases first beginning after the age of fifty than most other observers have reported.[5-10] There were 12 men and 8 women. In these cases the first symptoms developed in the sixth decade in 13 and in the seventh decade in 7. The onset was sudden in 8 cases (fulminating in 2) and gradual in the remaining 12.

A special effort was made to identify any factors responsible for precipitating the original or subsequent attacks of colitis. In 6 cases there was an associated severe emotional upset in family life or in business. A large overdose of a cathartic seemed causally implicated in 3 cases. One of these patients drank a full bottle of milk of magnesia and experienced a fulminating attack of ulcerative colitis, which subsequently required surgical treatment. Another, who took an excessive dose of agarol, required operation. Two patients were admitted to the hospital because of acute urinary retention, and exacerbations of colitis followed catheterizations. Three patients were given anticoagulant therapy, 1 for a suspected myocardial infarct and 2 for phlebitis (1 with pulmonary embolism), at a time when the colitis was quiescent, and all 3 suffered a severe reactivation of the disease, with grossly bloody diarrhea. One patient with a previous attack of colitis, who had been completely well for two years, was treated with cortisone for rheumatoid arthritis. On the sixth day of this therapy she had a fulminating attack of hemorrhagic diarrhea that, despite supportive transfusions, required emergency surgery to prevent exsanguination. Upper respiratory infections of a viral type preceded attacks of colitis in only 2 cases. This is in contrast to the findings reported in an earlier analysis of the precipitating factors in recurrences of ulcerative colitis for all age groups in which upper respiratory infections were implicated in 57 per cent of cases.[11]

The diagnosis on admission to the hospital was neoplastic disease of the bowel in 6 cases. In view of the age group and the nature of the intestinal symptoms this was an understandable error that served a good purpose in accelerating the necessary

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diagnostic studies. In 7 cases the diagnosis of idiopathic ulcerative colitis had already been established on the basis of sigmoidoscopic and radiologic examinations performed as office procedures. One patient was considered to have psychoneurosis on admission, and several others were believed to have functional problems during the early stages of the disease before hospitalization. The admitting diagnoses included diverticulitis, hemorrhoids, amebiasis and multiple vitamin deficiency.

TABLE 1. *Pertinent Data in Patients Treated by Medical Management Alone.*

CASE NO.	SEX	AGE AT ONSET	DURATION OF FOLLOW-UP STUDY SINCE ONSET	EXTENT OF DISEASE	CLINICAL COURSE	REMARKS
		yr.	yr.			
1	M	50	6	Descending colon	Single attack; patient asymptomatic to present.	Sudden onset suggested intestinal obstruction or perforated viscus
2	F	50	5	Descending colon	Two attacks, with asymptomatic 2-yr. interval; patient asymptomatic to present.	—
3	F	53	4	Entire colon	Single attack; patient asymptomatic to present.	Stormy attack, with marked depressed state
4	M	55	8	Descending colon	Three attacks in 4 yr.; patient asymptomatic for last 4 yr.	First attack; patient treated for piles by private physician; exacerbation of disease by catheterization of bladder and again by anticoagulant therapy for phlebitis and pulmonary embolism.
5	M	55	11	Sigmoidoscopic visualization	Single attack; patient asymptomatic to present.	—
6	M	56	11	Sigmoidoscopic visualization	Single attack; chronic constipation complaint to present.	Typical sigmoidoscopic findings 6 mo. before admission
7	M	59	6	Entire colon	Single attack; patient asymptomatic to present.	—
8	F	59	3	Sigmoidoscopic visualization	Single attack; patient asymptomatic to present.	—
9	F	61	2	Entire colon	Asymptomatic 2-yr. interval between 2 attacks, last resulting in death	10-month interval between sigmoidoscopic examinations revealed development of sigmoid polyp; permission for post-mortem examination refused.
10	M	65	8	Lower descending colon and sigmoid	Single attack; patient asymptomatic to present.	Polyps seen in descending and transverse colon 7 yr. after onset
11	F	67	1	Descending colon	Single attack	After upper respiratiory infection barium-enema examination for mild diarrhea revealed nonspecific superficial colitis; patient admitted to hospital with no symptoms of colitis for possible myocardial infarction; received anticoagulants, with hemorrhagic diarrhea resulting, barium-enema examination 4 mo. after 1st study showed severe ulcerative colitis.

It was evident that the age group of these patients was an important factor in delaying the prompt and accurate diagnosis of the disorder. It was noted that many of these patients in the later years of life lived alone and minimized or accepted their symptoms. They appeared to be poor observers and to seek medical attention late. The economic insecurity and unhappiness resulting from dispersion of the family circle led to emotional conflicts that often overshadowed their somatic complaints. They indulged in cathartic abuse. When they came for medical aid it was for unrelated organic disorders, usually referable to the genitourinary tract or the cardiovascular system, so that the associated colonic disturbance was frequently overlooked initially.

The symptoms on admission were those usually observed in this disease. All but 1 patient complained of abdominal pain, usually widespread and at times exceedingly severe, and 8 had had tenesmus. The stools were loose or watery in all but 2 cases, which were characterized by well formed stools. Sixteen patients had passed gross blood by rectum. Only 3 had been aware of fever before entry. Although 12 patients gave a history of weight loss, only 4 appeared thin and chronically ill on admission. The remainder of the patients were found to be well nourished, and 4 were listed as obese. Except for evidence of anal and perianal disease, physical examination did not reveal concurrent abnormalities. Six patients had anemia (hemoglobin of less than 12 gm. per 100 cc.), and 8 had leukocytosis (white-cell count exceeding 10,000). The total serum protein was less than 6 gm. per 100 cc. in 7 of the 13 cases in which this determination was made. Despite the foregoing observations, it is worthy of comment that most of the patients appeared only mildly ill on admission, whereas their subsequent course often tended to become serious and in several cases culminated in a major surgical procedure.

Sigmoidoscopy, which was performed in 17 cases, in each disclosed a typical acutely inflamed and friable, granular or edematous, hemorrhagic mucous membrane with punctate or diffuse ulcerations, presenting an appearance so characteristic as to be almost diagnostic in itself. The extent and severity of the ulcerative process proximal to the rectum was delineated most accurately by radiologic examination, which showed the entire colon to be involved in 6 cases (including the terminal ileum in 3), and

only the left half of the colon in 7. Three cases were segmental in type and localized to a portion of the descending colon, and 1 was limited to the rectum and sigmoid. There were no examples of right-sided colitis in the series. In 3 cases the radiologic findings in the colon were within normal limits although the sigmoidoscopic appearance was characteristic of the disease. On the basis of data compiled from the sigmoidoscopic and radiologic examinations and from the material obtained at operation and autopsy, it was found that 2 patients had discrete polyps of the adenomatous type, 8 had multiple pseudopolyps, and 1 had an adenocarcinoma of the colon.

In these patients a wide variety of associated diseases common to their age group frequently obscured or distorted the diagnostic pattern of the colitis and delayed its recognition. In many cases the coexistent lesion complicated the medical management considerably, but in no case did it influence the clinical course to a serious degree. Two patients had acute prostatic obstruction, 3 had acute rheumatoid arthritis, 1 had diabetes mellitus, 1 had an acute hypernephroma, 1 each had a duodenal and a gastric ulcer, and several had personality disorders. In addition, there was the usual incidence of cardiovascular disorders to be expected in this age group.

The medical management of these cases included the use of various combinations of the drugs and measures commonly employed in the treatment of nonspecific ulcerative colitis. Patients were given several modifications of a low-residue colitis-type diet, orally and parenterally administered vitamin supplements, injections of liver extracts, antibiotics such as penicillin and streptomycin, absorbable and nonabsorbable sulfonamides and supportive therapy such as intravenous fluid and electrolyte replacements, and transfusions of plasma and whole blood. Five patients received emetine or carbarsone empirically because of previous residence in localities known to be endemic for amebiasis. Symptomatic treatment included opiates in various forms, antispasmodics such as atropine and Banthine, and various sedatives. Several required decompression by the Wangensteen technic during the more critical stages of their illness. Two patients were given terramycin and 1 aureomycin later in the course of the disease, without any discernible clinical benefit. One patient received four doses of ACTH, and severe hemorrhages from the colon, requiring emergency resection, developed. Two patients were treated with cortisone, 1 for colitis, with a marked increase in the amount of rectal bleeding,

TABLE 2. *Data in Patients Operated On.*

CASE NO.	SEX	AGE AT ONSET	DURATION OF FOLLOW UP STUDY SINCE ONSET	EXTENT OF DISEASE	CLINICAL COURSE	REMARKS
		yr.	yr.			
12	M	50	7	Entire colon	2 attacks; single hospital admission, with death after operation.	Ileostomy performed, with postoperative complications of parotitis, jaundice, abdominal wall sepsis, and peritonitis
13	M	53	3	Left-sided colitis proximal to sigmoid adenocarcinoma	2 hospital admissions; mild diarrhea since operation.	Colostomy and subtotal colectomy; revision of colostomy 1 yr. later, when presence of colitis noted.
14	F	54	8	Descending colon	3 hospital admissions in 4 yr.; patient asymptomatic since operation, performed on last admission.	Cortisone induced exacerbation, with emergency ileostomy and subtotal colectomy
15	F	54	13	Entire colon	9 hospital admissions, with death after operation	Colostomy and subtotal colectomy; recurrent admissions for pyodermia and leg ulcers in addition to exacerbations of intrinsic disease; perisigmoid abscess found; small-bowel obstruction and peritonitis after operation.
16	F	55	4	Descending colon	2 hospital admissions; patient convalescing well since operation 5 mo. ago	Extensive bleeding after cortisone; ileostomy and subtotal colectomy; 7-mo. asymptomatic interval; peritonitis and wound ulcers, with stormy course and recovery after operation.
17	M	63	2	Localized to rectosigmoid	1 hospitalization 1 yr. after onset; asymptomatic 10 mo. after discharge.	Ileostomy; postoperative course particularly stormy, with small-bowel obstruction and electrolyte imbalance rapidly corrected and subsequent development of acute hydrops of gall bladder during convalescence successfully treated; revision of ileostomy required because of fistula and abdominal-wall abscess.
18	M	65	0.6	Entire colon	1 hospitalization, with death after operation	Ileostomy and total colectomy; ACTH given, with aggravation of hemorrhagic diarrhea requiring emergency surgery; parotitis, peritonitis and acute myocardial infarction after operation.
19	M	66	3	Localized sclerosed lesion, midportion of descending colon	1 hospitalization; patient asymptomatic; death 3 yr. later of uremia.	Local colonic resection; confusion of lesion with suspected carcinoma.
20	M	68	4	Localized ulceration and stenosis with involved descending colon	5 hospital admissions during 1st year; patient asymptomatic since then.	Colostomy and subtotal colectomy; colonic anastomosis performed on last admission.

and the other for rheumatoid arthritis two years after recovery from a first attack of ulcerative colitis, with prompt reactivation of the disease and the occurrence of massive hemorrhage.

Of the 20 patients who form the basis of this report, 11 responded to medical measures alone, and 9 eventually required one or more major surgical procedures (Tables 1 and 2). With few exceptions the patients treated medically ran a benign course in the hospital and reacted promptly and favorably to a conservative regimen. Only 2 of these patients experienced any further difficulty after the first admission. One patient was readmitted four years later for acute urinary retention and suffered an exacerbation of the colitis after catheterization. After recovery from this episode of colitis, phlebitis with pulmonary infarction developed, requiring readmission to the hospital. Treatment with heparin and Dicumarol resulted in reactivation of the rectal bleeding. The process eventually subsided, and the patient has remained asymptomatic for the ensuing four years. Another patient treated medically experienced a severe recurrence within a year and followed a progressively unfavorable course, with deterioration and depletion ending in coma and death. The medically treated patients have otherwise been asymptomatic for one to eleven years, with an average of five and six-tenths years.

The clinical course of the 9 patients who were operated on was much less favorable. Five required surgical treatment on the first admission. Three of these had emergency operations (for massive bleeding, suspected perforation or critically septic course). One had a localized resection of the descending colon for acute symptoms associated with marked segmental narrowing of the bowel considered at first to be neoplastic in origin but proved on pathological examination to be due to diffuse fibrosis secondary to chronic ulcerative colitis. One was operated on under similar circumstances and found to have segmental ulcerative colitis with an associated adenocarcinoma. In the remaining 4 surgical cases the patients had two to nine admissions before operation became advisable or imperative. The indications in 2 cases were progressive depletion with multiple complications, including rectal and perirectal sepsis, perisigmoid abscess, pyodermia and arthritis. One patient was operated on for subacute intestinal obstruction and had a partial resection for a stenosing lesion in the descending colon, which was due to a stricture in association with a previously known segmental ulcerative colitis. One patient with two earlier admissions for colitis required an emergency ileostomy and subtotal colectomy because of repeated massive hemorrhages that followed the administration of cortisone for rheumatoid arthritis. Of these 9 patients, 2 had an ileostomy alone, 3 had an ileostomy and subtotal colectomy, and 4 had segmental resections, usually in stages. Two patients subsequently required radical revision of the ileostomy because of fistula formation and sepsis of the abdominal wall, and another required revision of a colostomy because of failure to heal. There were 3 operative deaths from peritonitis and related complications. One of the surgically treated patients died three years later of uremia. The remaining 5 patients now appear to have completely recovered from colitis.

Discussion

It is evident that the incidence of nonspecific ulcerative colitis in people beyond the age of fifty as an initial and primary episode approaches 10 per cent of reported cases and is not necessarily related to the antecedent use of certain antibiotics in the therapy of other diseases. Contrary to expectation, emotional factors were as significant in the pathogenesis of the original and subsequent attacks in the older age groups as they are considered to be in the younger decades. Other precipitating factors of special importance in the elderly were found to be the gross abuse of cathartics, the use of anticoagulants in the management of thrombophlebitis and myocardial infarction, the administration of ACTH or cortisone for arthritis and the repeated catheterization of the urinary tract for acute retention. Before any of these measures are employed in the treatment of patients over fifty years of age, it is advisable to inquire closely concerning the existence of bowel disturbances. The effects of ACTH and cortisone in this group were especially unfavorable. These drugs were administered to 3 patients, with the prompt onset of serious hemorrhage in each. Similar complications have been reported[12,13] and perhaps appear with increased frequency in the aged. Further data on this point would be of interest.

The onset in many cases seemed deceptively mild and unimpressive owing to the stoicism of the patient or the presence of a more striking concurrent disease. It often gave no intimation of the extent or severity of the pathologic involvement or the unfavorable prognosis. This disparity between the mildness of the subjective complaints and the degree of pathologic change in ulcerative colitis among the aged has been noted by others.[4] The most common erroneous diagnosis on admission was carcinoma of the colon. In another reported series already referred to,[4] every 1 of 25 elderly patients with colitis was initially considered to have cancer of the bowel. It was probably the fear of carcinoma that impelled most of them to seek medical advice. The most important and accurate single diagnostic procedure was sigmoidoscopy, which revealed the true nature of the process in every case in which it was performed. Radiologic examination of the colon was invaluable to ascertain the full extent of the disease, to decide on the type of operation when surgery was indicated and to determine the presence of

inflammatory stricture or associated carcinoma. Reliance on a single x-ray examination performed early in the course of the disease could be misleading because of ostensibly negative findings. Since marked changes can appear subsequently within a comparatively short time, it is recommended that the examination be repeated when symptoms persist. The excellent state of nutrition of the group as a whole, notwithstanding the relatively advanced age of many of the patients, is worthy of note and makes it unlikely that dietary factors bear an important etiologic relation to the onset of the disease.

The extent of pathologic involvement bore no consistent relation to the prognosis. Some patients with involvement of the entire colon did remarkably well on medical management, and others with only the left half of the colon diseased required emergency surgery. The patients with typical involvement of the rectum as seen sigmoidoscopically but with negative x-ray examination of the remainder of the colon did uniformly well. The 3 patients with segmental disease were all treated by local resection, with excellent late results.

Despite the presence of both individual and multiple pseudopolyps, there was only 1 case of carcinoma in association with colitis. In this case the colitis was still present and active a year after resection of the tumor when the patient returned for revision of his colostomy. It appears that ulcerative colitis in this age group is not more prone to neoplastic complications than it is in younger patients. On the other hand, because of the disarmingly mild symptoms often present in colitis among older persons, an occult carcinoma can easily be overlooked unless a careful study of the entire colon is made. As noted previously,[14] it is usually impossible to distinguish the symptoms of carcinoma of the colon from those caused by an exacerbation of the colitis.

In general, the patients who responded well to medical management on the first admission have had only that single attack of the disease and no recurrences during the follow-up period. Of those requiring two or more admissions (6 patients) 1 has remained well after a second attack, 1 died of the colitis while on medical treatment, and 4 have been operated on. This suggests that the prognosis of colitis in persons of this age after recovery from one attack is good but with the second attack becomes guarded. This finding is at variance with the observations of others,[15, 16] who are of the opinion that the older the patient, the easier it is to control the disease. In an analysis of 129 cases of ulcerative colitis with the age of the patient ranging from five to sixty-eight years, Rice-Oxley and Truelove[9] came to the conclusion that age had little influence on the prognosis. In our own series of 20 patients, 9 required major surgery (ileostomy, subtotal colectomy, segmental resection), with 3 operative deaths. In addition to the high mortality in this small group there was a high surgical morbidity, with 3 secondary operations. The patients with segmental colitis presented the greatest difficulty in clinical diagnosis and therapeutic judgment because of confusion with diverticulitis and carcinoma. A case of this localized type illustrating some of the problems involved has recently been reported.[17]

On the basis of the foregoing observations, it is believed that patients with chronic ulcerative colitis beginning for the first time after they have attained the age of fifty represent a distinct group in whom certain precipitating factors may be of particular importance, early recognition especially troublesome and the clinical course remarkably benign or unusually severe and complicated.

Summary and Conclusions

Twenty cases of idiopathic colitis beginning after the age of fifty and followed from onset to the date of this survey are reported. This represents an incidence of 10 per cent of all patients with this disease admitted to the Beth Israel Hospital from 1941 to 1952 inclusive.

Among the factors implicated in precipitating the original or subsequent attacks were emotional stress, overdose of cathartics, administration of anticoagulants, use of cortisone and repeated catheterization for urinary retention.

Early diagnosis in many cases was hindered by the deceptively mild symptomatology, the stoicism of the patient, his excellent nutritional status and the coexistence of more impressive organic disease. Sigmoidoscopy was the most valuable single diagnostic procedure.

Eleven patients in their first attack responded promptly and favorably to the usual medical measures, and 10 of these were living and well an average of five and six-tenths years later. Nine patients required major surgical procedures (5 on the first admission), with a relatively high mortality rate. In the patients who survived operation the symptoms of the original disease have not recurred.

Ulcerative colitis beginning after the age of fifty years is often as serious and fatal a disease as it is in the younger age groups. Although in our experience the prognosis in the older patient after recovery from one attack is relatively good, with the advent of the second attack it becomes much more guarded.

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INHIBITION OF EXPERIMENTAL CHOLESTEROL ARTERIOSCLEROSIS BY ULTRAVIOLET IRRADIATION*

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IT is generally agreed that ultraviolet irradiation of cholesterol alters the physicochemical nature of this substance, although it is not clear what kind of process is responsible. Stavely and Bergmann,[1] and Mayneord and Roe[2] believe that some ozonide is formed, because cholesterol irradiated without access of oxygen or without moisture does not blacken photographic emulsions, whereas it does so if irradiated with access of oxygen or if moisture is present. Roffo[3] has maintained that, because of its oxidation after ultraviolet irradiation, cholesterol becomes carcinogenic. His assertion has not been confirmed by others.[4] Conversely, his contention that carcinogenic substances are formed on heating of cholesterol has received some confirmation.[5]

In 1950 Altschul[6] reported that irradiated egg yolk on being fed to rabbits was less effective in producing arteriosclerosis than the untreated material. Ultraviolet irradiation of pure cholesterol is also likely to decrease its noxious action when the product is fed to rabbits. On the other hand, the heating of either egg yolk or cholesterol increases its atherogenic property. Neither feeding or percutaneous application of heated or ultraviolet-irradiated cholesterol nor feeding of heated or irradiated egg yolk produced cancers in rabbits, white rats, guinea pigs, golden hamsters or prairie gophers.

The observation that ultraviolet irradiation decreases the atherogenic property of either cholesterol or egg yolk made it advisable to irradiate rabbits being given cholesterol in capsules during the experimental period. These experiments may have more than a theoretical value because of the great interest that cholesterol has received as a possible causative agent in human arteriosclerosis (according to Keys et al.,[7] "That the serum-cholesterol level is significant in relation to the development of atherosclerosis is now, of course, well established").

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MATERIAL AND METHODS

Eighteen rabbits (13 male and 5 female, and 8 colored and 10 albinos) received daily 0.3 gm. of pure cholesterol or of cholesterol heated for thirty minutes at 300°C. The cholesterol was ground up and filled into gelatin capsules, and a few drops of vegetable oil were added to facilitate absorption. The chemical analysis of the commercial cholesterol (Armour) showed that it contained at least 96 per cent digitonine-precipitable sterol giving the Liebermann–Burchard color reaction. The diet consisted of calf pellets, which are mixed after a balanced formula by the Quaker Oats Company of Canada. The animals also received oats, some hay and fresh greens. Sixteen of the 18 rabbits in the present experiment were from the same animal strains used in previous cholesterol experiments and bred in the same animal house of this department.

Seventeen animals were treated for ninety days; 1 sick animal had to be killed after seventy-one days. Their backs were shorn with electric clippers or depilated with a barium paste. This procedure was repeated at variable periods, depending on the growth of the hair.

The animals received ultraviolet irradiation three times each week. The source of irradiation varied, as did the time of exposure. All animals were irradiated at a distance of approximately 40 cm. The first 3 animals received the treatment for periods ranging from ten to twenty minutes, from a "Sun lamp" (275 watt). In the second group, the source of ultraviolet light was a Hanovia Utility Model, and the exposure was gradually increased from ten minutes to one hour. In the last two groups, a Burdick quartz lamp "Ultra Lux" was used, time and distance remaining the same as in the second group.

After ninety days (seventy-one in 1 case), the animals were killed by air injection or with nembutal. The lungs were fixed in situ by instillation of formaldehyde solution into the trachea, which was then ligated. The following tissues were taken for

examination: brain, pituitary gland, eyes, tongue, thyroid gland, lung, aorta, heart, thymus, skeletal muscle, skin, stomach, intestines, liver, spleen, pancreas and gonads. Stains mainly used were H. & E., iron hematoxylin-eosin and von Kossa's method for calcification.

In 14 animals the serum cholesterol levels (total, free and esterified) were determined at the beginning of the experiment and in all animals at the end.* In the last group of 6 animals, the white-cell count was followed throughout the entire experiment.† from the involvement of certain vascular territories that show lesions only if the cholesterol arteriosclerosis is extremely pronounced; from the participation of parenchymal tissues in the lipoidosis presenting a certain pattern, which aids in the classification of the intensity of the morbid process (the suprarenal cortex, for example, reacts very early and strongly, the liver cells change later and less intensely, whereas other epithelial structures are affected only in advanced cholesterol arteriosclerosis); and from the reaction of connective tissue and capil-

TABLE 1. *Effect of Ultraviolet Irradiation on Cholesterol Damage.*

EXPERIMENT No.	TYPE OF RABBIT	TOTAL SERUM CHOLESTEROL AT BEGINNING OF EXPERIMENT* mg./100 cc.	TOTAL SERUM CHOLESTEROL AT END OF EXPERIMENT* mg./100 cc.	MICROSCOPICAL FINDINGS
Group 1:				
1	Albino male	—	1240.0	Marked inhibition of cholesterol damage; only aorta and lingual artery affected; calcification in aorta; necrosis of suprarenal.
2	Brown female	—	1415.0	Slight, questionable inhibition of cholesterol damage
3	Albino female	—	690.0	Marked inhibition of cholesterol damage
Group 2:				
4	Albino female	—	300.0	Multiple abscesses; rabbit killed after 71 days; no inhibition of cholesterol damage.
5	Albino male	41	30.0	Only traces of cholesterol damage
6	Brown male	39	733.0	Marked inhibition of cholesterol damage
7	Brown female	110	570.0	Very slight cholesterol damage.
8	Brown male	53	367.0	Hardly any traces of cholesterol damage
Group 3:				
9	Albino male	36	100.0	Except for slight lipoidosis of suprarenal cortex, complete inhibition of cholesterol damage
10	Albino female	58	93.0	Except for slight lipoidosis of suprarenal cortex, complete inhibition of cholesterol damage
11	Albino male	60	25.0	Complete inhibition of cholesterol damage
12	Albino male	77	167.0	Except for slight lipoidosis of suprarenal cortex and few foam cells in aortic lining, no cholesterol damage
Group 4:				
13	Albino male	18	19.0	Very slight lipoidosis of suprarenal cortex; some intima fibrosis of aorta (?); no other changes.
14	Albino male	33	142.0	Lipoidosis of suprarenal cortex; necrosis of suprarenal cortex; calcification of aorta, with (secondary?) endothelial proliferation.
15	Brown male	49	51.0	Very slight lipoidosis of suprarenal cortex; no other cholesterol damage.
16	Brown male	60	22.5	Complete inhibition of cholesterol damage
17	Black male	94	434.0	Renal calcification; calcification of vessels. Slight cholesterol damage in aorta; endothelial proliferation in aorta and arteria lingualis; lipoidosis of suprarenal cortex.
18	Gray male	22	18.0	One small lipoid cushion in aorta; necrosis of suprarenal cortex.

*In all cases in which the total cholesterol was determined, the free and esterified relation was also established. Because after ultraviolet irradiation the relative values showed no significant shifts, they are omitted.

Several hundred rabbits fed cholesterol in previous experiments in this laboratory served as controls. For many of them, I used a standard procedure by giving daily 0.3 gm. of cholesterol in capsules for ninety days to animals weighing approximately 6 pounds. In all these animals, a considerable degree of arteriosclerosis was produced.

In the 18 irradiated rabbits, the intensity of the "cholesterol damage" was compared with that in nonirradiated animals that had been given the same amount of cholesterol by the same method (in capsules), and for the same period. The pathologic changes were assessed from the severity of single lesions (for example, the presence and quantity of foam cells in the aortic intima); from the thickness of lipoid cushions in coronary and lingual vessels; laries in various locations with different intensity and appearing at different times (further details concerning the procedure are given elsewhere[6]).

RESULTS

Macroscopical and microscopical examination of the tissues of rabbits receiving cholesterol and ultraviolet irradiation revealed, in the great majority of cases, a striking inhibition of cholesterol damage (Table 1), which should have occurred if cholesterol had been fed without ultraviolet treatment. The serum cholesterol at the end of the experiment showed a slight increase, or none, in the cases with little or no cholesterol damage (Table 1). In rabbits receiving for the same period the same amount of cholesterol without ultraviolet irradiation the serum cholesterol almost regularly surpasses 1200 mg. per 100 cc.

*Determinations performed by Mr. N. H. Tattrie, using the Schönheimer-Sperry method as modified by C. S. McArthur.

†Count performed by Miss M. E. Martin.

As reported previously[8] the number of white cells changes in the course of cholesterol arteriosclerosis of the rabbit, when a relative and absolute lymphocytosis occurs in the first stages and is followed by an absolute, and frequently relative, neutrophilia. In 6 cases (13 to 18) in which the cholesterol feeding was combined with intense ultraviolet irradiation, the white-cell count was currently determined, but no significant changes were found.

It is also worth noting that, in contrast to rabbits fed cholesterol without ultraviolet irradiation, the animals receiving cholesterol and irradiation suffered no loss of weight or depletion of fat tissue.

It was observed that the animals bore up well under the intense ultraviolet treatment. In some cases the skin showed a few fissures, and in the rare cases among the albinos in which the condition was severe, the intensity of the irradiation had to be decreased for a few days. In the first experiments, the animals were irradiated while being kept in a special wooden-frame structure. Later, they were left in their wire cages and could move freely while being irradiated from above. In spite of the fact that they stared for fairly long periods into the light, or at least did not turn their heads away, only a few of the albinos demonstrated conjunctival hyperemia, which disappeared without ill effect.

In 3 rabbits (Cases 1, 14 and 18), one of the suprarenal glands showed extensive necrosis. This has been observed in other cholesterol experiments,[6] but the incidence appears to have been higher in the present study. Although the number of cases is far too small to justify any conclusion, it is desirable to record these findings.

Discussion

Although the problem of ultraviolet irradiation of cholesterol has received much attention, the irradiation of animals fed cholesterol has been reported only by Rusch et al.[9] However, in their experiments only 1 rabbit was given cholesterol and ultraviolet irradiation whereas 5 other rabbits received cholesterol, combined with irradiation and inoculations with papilloma virus. The authors record that the treatment, which extended for thirteen months, did not inhibit arteriosclerosis. It is not my intention to compare their experiment with mine, because only 1 of their animals received cholesterol and ultraviolet irradiation and that for a much longer period. Only the aorta was examined for the presence of arteriosclerotic lesions. Particular attention was paid to xanthoma-like nodules, which were present in all cases. The blood cholesterol levels in their animals showed no decrease, although according to the experience of other workers,[10] "after two to three months the rise in serum-cholesterol levels off and is followed by a drop in spite of continued oral administration of cholesterol."

The influence of ultraviolet irradiation on cholesterol levels in man has previously been studied. Malcyński[11] has found that a single ultraviolet irradiation increases the serum cholesterol level in persons without cancer by 16 to 43 per cent, and in patients with cancer the ultraviolet irradiation is followed almost immediately by a decrease of 25 to 40 per cent in serum cholesterol. These findings were partly confirmed by Hubert,[12] according to whom, however, noncancerous diseases or pregnancy also shows a cholesterol decrease after ultraviolet irradiation, in a manner similar to that in cases of cancer.

On the basis of my investigation there seems little doubt that intense ultraviolet irradiation inhibits hypercholesterolemia, and mitigates or prevents cholesterol arteriosclerosis. I do not know whether the treatment would have the same results for long periods, thirteen or more months, as in the experiments of Rusch et al.[9] Nor do I maintain that irradiation will have the same effect in human arteriosclerosis. As is well known, in human arteriosclerosis the hypercholesterolemia never reaches the same high levels as it does in rabbits and therefore the irradiation may have little, if any, effect. Nevertheless, the influence on human atherosclerosis is worthy of further study in view of the steadily rising opinion that cholesterol is responsible for the atheromatous type of arteriosclerosis.

The following considerations regarding the possible action of the ultraviolet irradiation are offered:

The first is that an increase in vitamin D may inhibit cholesterol damage. Several workers have shown that vitamin D_2 increases the cholesterol effect. In a special investigation on rabbits, I could confirm this also for vitamin D_3.

Secondly, ultraviolet irradiation changes the physicochemical nature of blood cholesterol, whereby the latter loses its pathogenic property, similarly to steroid hormones, which lose their hormonal property after irradiation.[13]

Thirdly, the inhibition of a rise of serum cholesterol suggests that "lumicholesterol," which formed under the influence of ultraviolet irradiation, is readily excreted in contrast to cholesterol, and this factor may have had a decisive influence on my results. It could be objected that in view of the poor penetration of ultraviolet rays, direct effects on the cholesterol are hardly probable. But a microscopical examination of the epidermis from the back of the rabbit shows that the epithelium there is very thin.

Another explanation may be envisaged: it is believed that, under the influence of strong ultraviolet irradiation, living or dying cells produce "proliferation-promoting factors"[14] or "biostimulators,"[15] and these may, in some obscure way, affect cholesterol metabolism. My previous observation, however, that irradiation of either egg

yolk or cholesterol decreases its toxicity makes the last explanation rather improbable, and supports the second or third suggestion.

Summary and Conclusions

Previous experiments have shown that ultraviolet irradiation of cholesterol or egg yolk inhibits their atherogenic property. In the present investigation 18 rabbits were given cholesterol in capsules and exposed to irradiation for periods of ninety days (with 1 exception of seventy-one days). In 16, there was a marked or complete inhibition of that cholesterol damage that could be expected from the dose of cholesterol and from the duration of the experiment if no irradiation had been given. The inhibition of rise in serum cholesterol paralleled the microscopical findings. In 6 cases the white-cell picture was followed throughout the experiment and showed none of the changes seen in cholesterol arteriosclerosis.

In the explanation of the inhibitory action of ultraviolet irradiation, the role of vitamin D can be excluded. The change of cholesterol to lumicholesterol may render it less noxious or more easily excreted so that it will not accumulate in the fluids and tissues of the body. Although this explanation seems to be the best founded, a production of protective substances of obscure structure and function (proliferation-promoting factors and biostimulators) is envisaged.

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MEDICAL PROGRESS

POSTOPERATIVE THROMBOPHILIA*

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Postoperative thromboembolism is a modern disease. The earliest mention of phlebitis is commonly accepted as being that of Aretaeus,[1] who described in the first century B. C., the autopsy on a patient with inflammation "about the vena cava." The account, however, is not sufficiently complete for one to know whether the condition was in fact thrombophlebitis in the modern sense of the term or some retroperitoneal infection such as a psoas-muscle abscess. It seems apparent, however, that for the eighteen hundred years that intervened between Aretaeus and Virchow[2] phlebitis was considered to be a septic process and was mentioned most frequently in connection with swollen arms after phlebotomy or with puerperal sepsis.

Bland thrombi, later well described by Aschoff,[3] had, it is true, been recognized and occasionally termed "marantic thrombi" since they were frequently associated with depleted states. But these were not considered to be related to "phlebitis" until Virchow suggested that the initiating factor in that condition was the thrombus itself.

Postoperative phlebitis seems first to have been reported in 1818 by Carmichael,[4] who described 3 cases; Puchelt,[5] in 1844 collected from the literature several cases that had followed amputation of the cervix, cutting for stone and amputation of limbs. Full recognition of surgery as an important precipitating cause of thrombosis and embolism waited, however, until the opening of the era of abdominal surgery at the end of the nineteenth century.[6]

With the recognition of surgery as a predisposing factor attempts at identification of etiologic agents were made. Earlier writers, such as Hunter,[7] Hewson[8] and Magendie,[9] searching for causes of thrombosis, had done so by attempting to explain the coagulation of blood outside the body and had discussed the effects of cooling, exposure to air and carbon dioxide on blood coagulation. Virchow[2] was the first to consider alterations in coagulation factors, of which he mentioned fibrin, to be one of the

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three causes for thrombosis, the other two being stasis and endothelial injury. Eberth and Schimmelbusch[10] demonstrated that platelets migrate to the peripheral part of the blood stream during slowing of the flow, and Aschoff considered "qualitative and quantitative alterations" in the platelets to be of importance in thrombosis. It was not until 1927, however, that Hueck[11] demonstrated a thrombocytosis during the second postoperative week, a phenomenon that was preceded by a transient thrombocytopenia, and so presented the first objective evidence of postoperative alterations in any of the coagulation factors.

Current knowledge of the subject was reviewed in 1950.[12] The most important alterations that emerged from the review were the changes in platelets similar to those that Hueck described. An increase in fibrinogen and another procoagulant substance, probably thromboplastin, also seemed established, as did a concomitant decrease in the plasma prothrombin conversion accelerators. In the last two years work in the field has continued to a point where a further progress report is timely. New techniques, determination of the coagulation time in silicone tubes, the use of ACTH or cortisone to mimic the "stress" associated with operation, procedures for the study of accessory factors in the prothrombin complex and a new method of studying blood viscosity in its relation to coagulability have appeared.

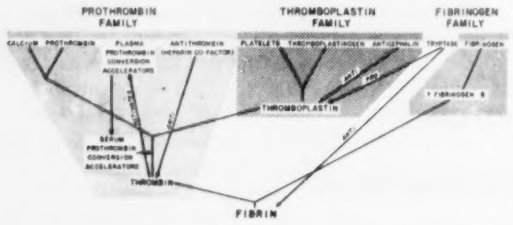

FIGURE 1. *Substances Involved in the Coagulation Mechanism.*

MECHANISM OF COAGULATION OF THE BLOOD

Although during the last two decades new coagulation factors have been discovered, and some previously suspected have been further defined, it is convenient to maintain the basic concept of blood coagulation that stems from 1904, when various workers, of whom Morawitz[13] has been the most widely cited, described the biphasic nature of the process, the first phase being the interaction of calcium, prothrombin and thromboplastin to form thrombin, and the second that of thrombin and fibrinogen to form fibrin.

To conform with Morawitz's theory it is convenient to consider the numerous additional substances subsequently shown to be important in the coagulation mechanism as members of families of which prothrombin, thromboplastin and fibrinogen may be called the heads. Figure 1 demonstrates this grouping. It is to be noted that calcium has been made a member of the prothrombin family, since there is evidence[14] that it forms a calcium prothrombinate after uniting with prothrombin early in the coagulation process. The inclusion of the prothrombin conversion accelerators, of antithrombin and of heparin cofactor in the prothrombin family is unquestioned, as is that of platelets, thromboplastinogen and anti-

COAGULATION TESTS

SPECIFIC TESTS	NONSPECIFIC TESTS
PROTHROMBIN FAMILY	COAGULATION TIME IN GLASS
CALCIUM	COAGULATION TIME IN SILICONE
PROTHROMBIN	RECALCIFICATION OF PLASMA
PROTHROMBIN CONVERSION ACCELERATORS	HEPARIN TOLERANCE AND RESISTANCE
ANTITHROMBIN	SERUM PROTHROMBIN
THROMBOPLASTIN FAMILY	THROMBIN DEGRADATION
PLATELET COUNT	VISCOSITY
MEGAKARYOCYTE ACTIVITY	PROTAMINE TITRATION
FIBRINOGEN FAMILY	
FIBRINOGEN	
FIBRINOGEN B	

FIGURE 2. *Tests Employed to Determine Coagulation.*

cephalin in the thromboplastin family. Fibrinogen and fibrin comprise the fibrin family. Plasma tryptase or protease alone remains an orphan since it may act as both a thromboplastin and a fibrinolysin.

A detailed description of the manner in which the various elements act and interact and the evidence for such statements are beyond the scope of this review. Figure 1 is presented not as a new theory of blood coagulation but as a graphic list for purposes of reference.

STUDIES OF COAGULABILITY

Methods and tests used to evaluate blood coagulability and its individual factors are conveniently divided into two types. These are specific tests, which measure, or purport to measure, concentrations of individual coagulation factors, and nonspecific tests, which measure alterations in coagulation brought about either by unknown factors or by two or more factors acting together. A list of the procedures employed in the study of these factors is presented in Figure 2.

Data on alterations of blood coagulability in the operative or postoperative period have been obtained by two types of experimental approach, which may be called the direct and indirect. The direct method has consisted of observations on the blood of patients during or after surgical operations. Indirect methods have comprised similar observations in

man or in animals that have undergone alterations in physiologic homeostasis induced by factors assumed to be involved in surgical operations, such as apprehension, increased circulating epinephrine, administration of ACTH and cortisone, hemorrhage, anesthesia and trauma in addition to that of the operation. Which of the two methods will eventually be more fruitful is unknown. A surgical operation represents such a complex of the influences of drugs, anesthesia, trauma, blood loss, varying degrees of anoxia, stress, endocrine factors and alterations of fluid and electrolyte balances that at present it is essential to consider both methods of study.

Specific Tests

Prothrombin Family

Calcium. No significant changes in serum calcium concentration have been reported as occurring after surgical operation. Furthermore, no evidence has been forthcoming to alter the impression that the changes in calcium ion postoperatively could be so great as to be fatal through the coagulation mechanism or for other reasons.

Prothrombin. As previously stated[12] hypoprothrombinemia after surgical operation has been consistently observed by workers who have used methods for prothrombin determination that employ whole plasma.[15-17] The hypoprothrombinemia is maximal during the first week. A later rise of prothrombin activity has been found by Shapiro,[17] but not by the other workers mentioned. Other observers, using dilution methods for prothrombin determinations, have detected hyperprothrombinemia in the early postoperative state.[18, 19] On the other hand changes in prothrombin activity postoperatively were not found by Allen,[20] by Borgström[21] or by Fowler.[22] These discrepancies suggest that the dilution and the whole-plasma methods of prothrombin determination do not measure identical substances.

Prothrombin conversion accelerators. The term is used as a composite to include indiscriminately all the accessory factors, other than prothrombin itself, that have prothrombin activity. At least four of these have been described under different names. Owren[23] has called them proaccelerin, proconvertin, accelerin and convertin. The term prothrombin conversion accelerators is perhaps less appropriate than that of "prothrombin accessory factors" since it seems clear[24] that these substances are essential to prothrombin conversion rather than merely accelerators of it. Since I have used the term before, however, I continue, in the interests of consistency, to do so here. Few studies of the postoperative behavior of prothrombin conversion accelerators are available. Warren et al.[25] and Stefanini[26] found them to decrease significantly in the early postoperative period. Different methods were used by the two observers, both of whom, it is assumed, were measuring primarily proaccelerin, although in Warren's method the measurement of some proconvertin activity cannot be excluded.[27] It is probable that the apparent decrease in prothrombin activity in the postoperative state noted by those workers who use whole plasma methods for prothrombin estimation is largely due to a deficiency of prothrombin conversion accelerators. Whether the deficiency is due to hemorrhage or to the consumption of the factor during the blood coagulation necessary for surgical hemostasis has not been determined. Preliminary observations suggest that it is unrelated to liver damage.[27] Since specific methods of analysis of the prothrombin conversion accelerators are now available[23] it is hoped that they will soon be applied to the study of postoperative thrombophilia.

Antithrombin. In the 1950 review it was noted that Kay[28] had confirmed the work of Boshamer[29] in detecting a decrease in the plasma antithrombin in the postoperative state, whereas others[30,31] found either an increase or no change. An attempt to discover consistent changes in postoperative antithrombin has been made in this laboratory[27] using the method of Astrup and Darling.[32] Decreases in antithrombin were rarely noted; similar patients demonstrated opposite changes, and marked fluctuations from day to day in the postoperative period were common.

Thromboplastin Family

Platelets. The early postoperative fall in platelets that precedes the later rise described by Hueck and later confirmed by others has recently been shown to begin as early as two hours after the onset of surgical operation.[33] The increased adhesiveness of platelets at the time of the thrombocytosis of the second postoperative week, as originally described by Wright,[34] has been confirmed.[33] The potentiality of thrombosis is therefore doubly great at this time.

Furthermore, Kerhulas,[35] in his studies of bone-marrow biopsies, found an increased production of platelets by the megakaryocytes on the tenth postoperative day at the time of the height of the platelet tide. This finding not only completes the concept that the increase in platelets is actually due to bone-marrow hyperactivity but also helps to corroborate Wright's opinion that the larger the number of young platelets present the greater the adhesiveness of the platelets in the sample.

Fibrin Family

Fibrinogen. No new knowledge has been added in the past few years to understanding of the postoperative behavior of fibrinogen. A moderate to marked increase in the plasma fibrinogen level between the third and the ninth postoperative day[12] has generally been observed.

Fibrinogen B. An intermediary substance liberated by the conversion of fibrinogen to fibrin has

been described by Lyons[36] and found to be present in the blood of postoperative patients as well as those having tissue necrosis from any cause. Cummine and Lyons[37] set up criteria by which the fibrinogen B test could help them predict which patients would have thrombosis. Others[38-40] have found the results of the test to show increased values in situations in which tissue necrosis had occurred but were unable to predict thrombosis by means of it and have questioned whether fibrinogen B is as distinct from fibrinogen as Lyons and his co-workers suggest.

Nonspecific Tests

Coagulation Time

The introduction of the silicone coagulation test by Jaques[41] based on the earlier work of Lee and White[42] as a convenient method of rendering the walls of test tubes nonwettable and so protecting the platelets against agglutination has resulted in wide use of the method in many situations in which protection of platelets against disintegration is desired.

One such situation is the determination of the coagulation time. The normal coagulation time for whole blood in a silicone tube varies between forty and ninety minutes rather than seven to twelve minutes as has been customary in glass.[27, 41, 43] Unfortunately, the normal silicone coagulation time varies depending on what sort of silicone is used and upon the care and the method by which the blood is taken. Furthermore, the blood, being practically immune to spontaneous thromboplastic initiation of blood coagulation, is more vulnerable to the error of contamination with a small amount of thromboplastin than the glass method is. To follow further this train of thought one might well ask what the substance is that initiates the clot under these circumstances. The answer is that, presumably, some degree of platelet damage eventually occurs, and that there is no evidence that, merely because it is less in degree, it is more controllable in silicone than in glass.

McCleery[43] has demonstrated a most consistent performance with the method and found no alterations in a large group of postoperative patients, except in those in whom thrombosis had already begun when the silicone coagulation time was significantly shortened. He considers it to be of value in the differential diagnosis of conditions in which thrombosis is not clinically clear. Fowler[22] also found no changes in the silicone coagulation time in a group of nonthrombophilic postoperative patients selected at random.

Coagulation Times under the Influence of Heparin

Since de Takats[44] introduced a technic of studying the coagulation time under the influence of heparin numerous observations on the results of that test and its modification have been reported. The heparin has been either injected into the patient before the blood has been drawn[44] or placed in the test tube into which the blood is drawn.[45] The coagulation times have been determined either on whole blood or on plasma by means of recalcification.[46] Results have been conflicting. In 1943, for example, de Takats found a tendency to hypercoagulability in the first three postoperative days with the heparin tolerance test in which the heparin is injected into the patient. More recently, however, using a test in which the heparin is added to the blood in vitro, he observed two types of response in different groups of patients, one showing hypocoagulability and one showing no change. Others, however, using these methods or modifications[12, 22, 45-47] have noted a tendency to hypercoagulability during the first postoperative week. Dejardin and Mascart[48] also found a marked change of the heparin clotting time toward hypercoagulability twenty-four hours after operation.

The mechanism of altered reactivity of the blood to heparin is not entirely clear. Since thromboplastin and heparin seem in vitro to be mutually antagonistic many have postulated that changes in the action or the potential of the thromboplastin family were the chief factors in changing the heparin-retarded coagulation time. The experimental evidence of Hartmann,[49] however, has demonstrated no alteration of heparin tolerance in dogs given thromboplastin (brain suspension) intravenously. The action of heparin in causing an apparent decrease in the accelerators of prothrombin conversion has recently been observed by Belko.[50] It is possible that minor deficits in the prothrombin complex are responsible for heparin hypersensitivity. Causes of varying heparin tolerance and resistance must await further study. Suffice it to say that despite de Takats' more recent work the body of evidence produced by this test is in favor of a trend to hypercoagulability in the early postoperative period and that thromboplastic activity is certainly one of the chief factors responsible for its end-point.

Serum Prothrombin

No further reports on changes in serum prothrombin in the postoperative state have been forthcoming since that of Warren and Belko,[25] who found a significant increase in prothrombin consumption during the first three postoperative days that was suggestive of an increased activity in the thromboplastin mechanism. The serum prothrombin determination is perhaps more indicative of alterations in this mechanism than the heparin resistance tests are, since the former is significantly altered in certain clinical conditions, chiefly thrombocytopenic purpura and hemophilia,[51] in which the thromboplastin mechanism is deficient, whereas the latter are not. It again indicates a tendency to hypercoagulability in the early period.

Thrombin Degradation Rate

Fontaine et al.[19] reported observations on the use of a test that detects the speed of disappearance of thrombin from the serum of recently drawn and defibrinated blood; the amount of thrombin was measured by the extent to which serum affects the recalcification time of the patient's citrated plasma thirty minutes and sixty minutes after the sample had been drawn. It was found that the speed of thrombin degradation was slightly decreased in blood drawn from patients in the postoperative state. The test used was in principle a modification of other tests for measuring serum "prothrombin," which are known to show values that decrease as time elapses after coagulation. Quick[52] has shown that the degradation of serum prothrombin is considerably slower after coagulation in patients with hemophilia than in normal persons. Fontaine's is the only observation, to my knowledge, on such changes in the postoperative state. It is of interest that in the conditions in which Quick found a delayed disappearance of serum "prothrombin" in the first hour after clotting the assumption was that this was evidence of hypocoagulability whereas in Fontaine's test a similar delayed disappearance of "thrombin" was interpreted as being evidence of hypercoagulability.

Viscosity

The relation of blood viscosity to coagulation has in the past not been well clarified. Shadid[53] observed a high viscosity index in patients undergoing thrombosis in whom a simple method of testing was used. The recent development, by Yesner et al.,[54] of a method of detecting change in viscosity by electrically determined variations of resistance to a probe vibrating at ultrasonic frequencies in the test medium has provided a means that gives promise of detecting hypercoagulability before the occurrence of coagulation. That viscosity as measured by this device and coagulability go hand in hand was demonstrated in the form of clinical experience with a patient with pseudohemophilia, with another with an unidentified bleeding tendency and with the blood of patients under the influence of anticoagulants. Increased viscosity in postoperative periods was observed.

Blood Heparinoids

There has been persistent disagreement about whether heparin circulates normally in the blood stream. Since it has been found that protamine will neutralize heparin and that toluidine blue, which stains selectively the granules in the mast cells, acts in a similar manner, both these materials have been used to titrate possible heparin or heparin-like substances (heparinoids) in the blood. Increased values have been observed in certain pathologic states such as leukemia[55] and anaphylactic shock,[56] but the meager data available on the use of these tests in the postoperative state have been conflicting. Buonomo La Rossa,[57] for instance, using toluidine blue to titrate the blood heparinoids, found a decrease, whereas LiVoti,[58] using protamine, found an increase in postoperative patients. The reason for this disagreement is not apparent.

Observations on Conditions Related to or Simulating Operations

Stress

Studies of the metabolic response to the trauma of surgical operation have indicated that much of the altered pattern of normal values is similar to that which is produced by increased adrenocortical activity. Moore[59] has shown that the movements of electrolytes and water after operations can be closely simulated, although not exactly reproduced, by injections of ACTH.

Studies of alterations in coagulation that follow the administration of ACTH or cortisone and during states of adrenal hyperfunction have been performed. With one exception[60] workers who have studied the prothrombin mechanism have found no alterations in prothrombin or prothrombin conversion accelerators.[61-63] McGraw, Margulis and Brush,[60] using large daily doses of 200 to 300 mg., demonstrated a rapid fall in prothrombin activity, which later returned to normal while the patient was still on the drug.

Studies of the thromboplastin mechanism have not been widely undertaken in patients under ACTH or cortisone therapy. Prothrombin consumption (serum prothrombin) tests have been normal. It is surprising that, although it has become finally established that administration of the drugs would cause thrombocytosis in patients with thrombocytopenic purpura or other hypersplenic states,[64, 65] studies of the platelets in normal persons under the influence of drugs have been few. Koller and Zollikofer[66] found the platelets to increase after ACTH administration in 4 normal persons, but examination of their data shows that in 2 of the 4 there was an initial transitory decrease. Daily doses of 25 mg. were used. Nelson[62] also noted predominantly a rise in platelets after injection of the drug. Lauridsen et al.,[67] however, reported a definite decrease in platelets occurring within two hours of ACTH injection and lasting eight to sixteen hours, returning to normal appreciably before the eosinophils did. If the ACTH was given on three successive days in decreasing doses a platelet curve similar to that of the first postoperative week was obtained. Others[61, 63, 68] have found no change in platelets after the drugs have been given. Further work is needed to explain these discrepancies.

Fibrinogen has been shown to decrease slightly in arthritic patients treated with ACTH, concomi-

tant changes occurring in the sedimentation rate.[69] Cosgriff[63] found no deviations of the fibrinogen B determination after ACTH injection.

The coagulation time, determined in glass by the Lee–White method, was significantly shortened in 8 of 10 patients who had thromboembolic manifestations while on ACTH therapy, according to Cosgriff.[63] Fahey,[70] however (using a method in which blood was drawn in oiled syringes so that the normal clotting time was twenty-five to forty minutes), found no change after ACTH administration nor in a patient with Cushing's syndrome. The doses used by Fahey were 20 to 50 mg. a day and those used by Cosgriff up to 100 mg. a day. Napolitano's[61] results were the same as Fahey's on daily doses of 50 mg. intramuscularly or 8 mg. intravenously. Chevallier[71] confirmed these observations. Monto et al.[68] observed, however, in 3 normal persons given only 25 mg. of ACTH, a prolongation of the coagulation time.

The heparin tolerance and resistance tests done after ACTH or cortisone injection have been studied by de Takats,[72] who found variable results characterized by either a tendency to hypocoagulability or no changes, whereas Cosgriff observed the Waugh-Ruddick test, which is nearly the same as that used by de Takats, to change toward hypercoagulability in 4 of 6 patients exhibiting thromboembolic phenomena on ACTH.

Circulating heparin-like substances seemed to be increased early in a course of ACTH therapy according to Margulis[73] but often returned to normal soon thereafter. Warren et al.[74] have found little change in such titrations under the influence of ACTH.

These results suggest that the methods of measuring coagulation time still differ in different hands and can only be relied upon when alterations are exceedingly great.

Hemorrhage

The effects of hemorrhage on the blood coagulation mechanism have been studied since the time of Hewson,[75] who observed in animals and man during phlebotomy that "the blood which issued last coagulated first." In 1909 von den Velden[76] repeated the work, made the same observations and postulated that hydremia resulting from interstitial fluid entering the vascular bed transported thromboplastin from the tissues. McClintock and Magers[77] reported that the shortening of the coagulation time after hemorrhage did not occur if the spleen had previously been removed. They deduced that when the spleen contracts as a result of hemorrhage it liberates a coagulation factor into the blood stream.

Gray and Lunt[78] found shortening of coagulation times from seven to two and a half minutes in cats that were bled of 13 per cent of their blood volume. Shafiroff et al.[79] observed hypercoagulability after experimentally induced hemorrhages in dogs. Studies of various blood coagulation factors after loss of 500 to 1500 cc. of blood in human beings by Warren et al.[33] showed no alteration in the clotting times. The plasma prothrombin values, however, were decreased to 60 or 70 per cent. Platelets were not affected. de Takats[80] described an elevation of the sensitized clotting time in patients with massive hemorrhage.

Anesthesia

The isolated effect on the coagulation mechanism of an anesthesia of the duration and depth of that used in a major surgical operation has not been studied in human beings. The concomitant surgical operation has always interfered with the experiment. In dogs, Searles[81] found a slightly increased coagulability of the blood as measured by the coagulation time and a slight increase (in the range of 80,000 per cubic millimeter) in circulating platelets when ether anesthesia was given. Levy and Conroy,[82] using the Smith bedside method of prothrombin determination, noted a significant shortening of the time (increase in prothrombin activity) after induction of full ether anesthesia in 50 patients; there was no change in 25 patients given spinal anesthesia. Gilmore et al.[83] reported a shortening of the coagulation time done on the tail blood of rats given nitrous oxide if less than 10 per cent oxygen was administered, and considered that hypoxia tends to cause increased coagulability. Significant abnormalities were not noted in the coagulation time or prothrombin activity of 2 patients given ether anesthesia for the manipulation of stiff joints due to arthritis.[12] French and his associates[84] observed a moderate decrease in prothrombin as a result of ether or cyclopropane administration in patients with abnormal livers.

Thrombosis

Since a considerable amount of thrombosis must occur within the damaged vessels as an inevitable consequence of surgical incisions and dissections, a review of the data available on alterations in coagulation attendant on intravascular thrombosis is of interest. Those who have found significant alterations at the time of thrombosis have noted that they were in the direction of hypercoagulability. McCleery et al.,[43] Cosgriff[63] in studies on human beings and Nelson,[62] working with dogs, reported the coagulation time of whole blood to be shortened in the majority of cases of acute thrombosis. Fowler,[22] however, observed no change in the coagulation time in a single patient in whom phlebitis developed under his observation.

Changes in prothrombin have been less consistent. Mahoney and Sandrock[16] reported hyperprothrombinemia, or at least a lack of the customary hypoprothrombinemia that follows surgical oper-

ations, in patients who manifest thrombosis. McClure[85] and McCleery[43] found the test to be falsely positive in 45 and 42 per cent respectively of their cases of thrombosis, and Nelson[62] did not detect any alterations in prothrombin activity in active thrombosis. Fontaine[19] joins with Mahoney in observing a hyperprothrombinemia in most cases.

Holden,[31] Kay[28] and Boshamer[29] all described excessive falls in heparin cofactor or plasma antithrombin in patients in whom thrombosis developed. McLachlin[56] found no antithrombin changes in 8 of 10 patients at the onset of thrombosis.

During the active phase of thrombosis the sensitized clotting time (in vitro heparin resistance) of de Takats was shortened in most cases. In the uncertain state of knowledge one does not know whether to expect findings in the peripheral blood that demonstrate an increase in the forces of coagulation because of their being mobilized or whether the values should be diminished secondary to the consumption of coagulation materials. Many observations made on the coagulation time of whole blood, serum prothrombin and plasma prothrombin in this laboratory on patients with active thrombosis have in general shown inconclusive results. There has been a slight tendency, in cases that have shown significant changes, to a pattern found in the early postoperative state — namely, a lowered platelet count and serum prothrombin (increased prothrombin consumption). The importance of finding a test to detect the prethrombotic state or the presence of subclinical thrombosis is obviously great. The ability thus to establish a definite diagnosis of intravascular thrombosis would make attempts at specific therapy more effective in patients in whom the diagnosis is otherwise in doubt. To date, however, none of the alterations mentioned have been sufficiently exaggerated or consistent to serve this purpose.

Discussion

This review has confined itself to an analysis of what up to the present has been learned about postoperative alterations in blood coagulation. The fact that these influences represent only one aspect of the problem of postoperative thrombosis has not been overlooked. It is recognized that the parts played by venous stasis and intravenous mechanical factors are undoubtedly important, perhaps even more so than the matters discussed.

It is apparent that many of the technical methods used in the study of coagulability are to some degree inaccurate. Numerous modifications of each method exist. Seldom, in fact, do two laboratories use exactly the same one in the study of a single factor.

In general, however, the postoperative period seems to be divided into two parts, the early and the late, each one occupying approximately a week. During the early period a decrease in prothrombin conversion accelerators and a thrombocytopenia occur; on the other hand the coagulation time of whole blood, whether in glass or silicone or whether with added heparin, is shortened, antithrombin activity is decreased, and prothrombin consumption is increased. During the later postoperative period the prothrombin conversion accelerators return slowly to normal, thrombocytosis occurs, prothrombin consumption and antithrombin return to normal, and fibrinogen, which has begun to rise in the mid-early period, remains elevated until the ninth or tenth day, when it also returns to normal.

Although much work needs still to be done available information suggests that, whereas factors of stress and tissue trauma are equally important in causing these alterations, those of anesthesia and hemorrhage — of the degree, at least, incurred in the usual operation — are relatively insignificant.

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MEDICAL INTELLIGENCE

AGENESIS OF THE LUNG AND PATENT DUCTUS ARTERIOSUS WITH REVERSAL OF FLOW*

Report of a Case

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AGENESIS of a lung is a rare developmental defect that is usually not recognized until after death. In the majority of the 57 cases reported the diagnosis was made at autopsy.[1-3] Before 1942 the diagnosis was made correctly before death in only 3 cases; since then it has been made in 18 living patients.[1-4] The increased frequency of ante-mortem recognition is probably due to the wider use of bronchoscopy, bronchography and angiocardiography in the investigation of obscure pulmonary conditions.[3]

Pulmonary agenesis is commonly associated with congenital anomalies of other organs, including the heart.[1-3] Its association with a patent ductus arteriosus, which was recognized after death of the patient at the age of four months, has been reported in only 1 case.[4] In the living patient described below congenital absence of the left lung and a patent ductus arteriosus were suspected clinically and conclusively identified by angiocardiography, cardiac catheterization and bronchography. A feature of particular interest was the presence of reversal of flow through the ductus.

CASE REPORT

A 22-year-old Iranian student (N. Y. H. 623,426) gave a history of progressive exertional dyspnea since the age of 2. From early childhood the left side of the chest had been smaller than the right. For 8 years he had noted clubbing and cyanosis of the toes, without similar changes in the fingers. An x-ray film of the chest, taken at the age of 7 because of recurrent respiratory infections, was interpreted as showing a "collapsed left lung."

Physical examination revealed a short, hyposthenic man. The trachea deviated to the left; the left hemithorax was smaller than the right and expanded poorly. Breath sounds over the left side of the chest were diminished. The heart was displaced to the left, and the right cardiac border was percussed 1 cm. to the left of the sternum. Varying murmurs were heard. On one occasion a faint systolic murmur was heard in the 2nd left intercostal space and in the interscapular region. On another, presystolic and loud rumbling diastolic murmurs were heard in the left axilla. The finger-nail beds appeared plethoric but not cyanotic; the toes were clubbed and cyanotic.

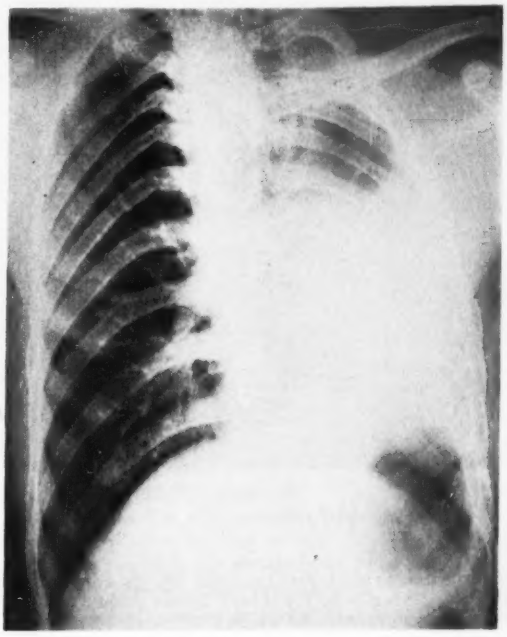

FIGURE 1. *Conventional Posteroanterior Chest Roentgenogram. A homogenous density fills the lower half of the left side of the chest. The trachea is displaced to the left, as is the heart. A bronchogram (not shown here) revealed absence of the left main bronchus.*

Examination of the blood showed a red-cell count of 7,700,000, with a hemoglobin of 21.7 gm., and a hematocrit of 70 per cent. An electrocardiogram (unipolar limb and chest leads) disclosed changes consistent with marked clockwise rotation of the heart and hypertrophy of the right ventricle. In the conventional frontal roentgenogram (Fig. 1) the left hemithorax appeared underdeveloped. The trachea and heart were markedly displaced to the left. It was not possible to identify

TABLE 1. *Data Obtained by Cardiac Catheterization.**

SITE	BLOOD OXYGEN CONTENT	PRESSURES			OXYHEMOGLOBIN SATURATION
		SYSTOLIC	DIASTOLIC	MEAN	
	vol. per cent				%
Pulmonary artery	20.3	113	70	92	—
Right ventricle (outflow tract)	19.5	113	5	—	—
Right ventricle (inflow tract)	19.2	—	—	—	—
Right atrium	19.1	—	—	3	—
Superior vena cava	20.6	—	—	—	—
Right brachial artery	27.6	—	—	—	94.1
Right femoral artery	24.0	117	70	79	84.1

*Other data included pulmonary blood flow of 2.18 liters per minute per square meter, and left-right shunt of 0.47 liter per minute. Body-surface area was 1.53 square meters.

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the great vessels and cardiac chambers in the homogenous density that occupied the lower two thirds of the left side of the chest. The upper third appeared to contain normal lung. A bronchogram revealed absence of the left main bronchus. In the angiocardiograms (Fig. 2 and 3) the density in the left side of the chest was seen to be composed entirely of cardiovascular structures. The superior vena cava, right atrium and ventricle were displaced to the left of the thoracic spine and rotated clockwise. The main-stem pulmonary artery and all its ramifications to the right lung were greatly dilated. The lung tissue in the upper left part of the chest was supplied by a branch of the right pulmonary artery and was thus demonstrated to be herniated right lung. The left pulmonary artery was absent; in its place was a short patent ductus arteriosus, 16 mm. in diameter. The descending aorta was opacified through the ductus at time of filling of the pulmonary artery with contrast substance; this indicated right-to-left blood flow through the ductus. Persistent opacification of the pulmonary artery at time of filling of the left ventricle and ascending aorta suggested that left-to-right shunt through the ductus also existed.

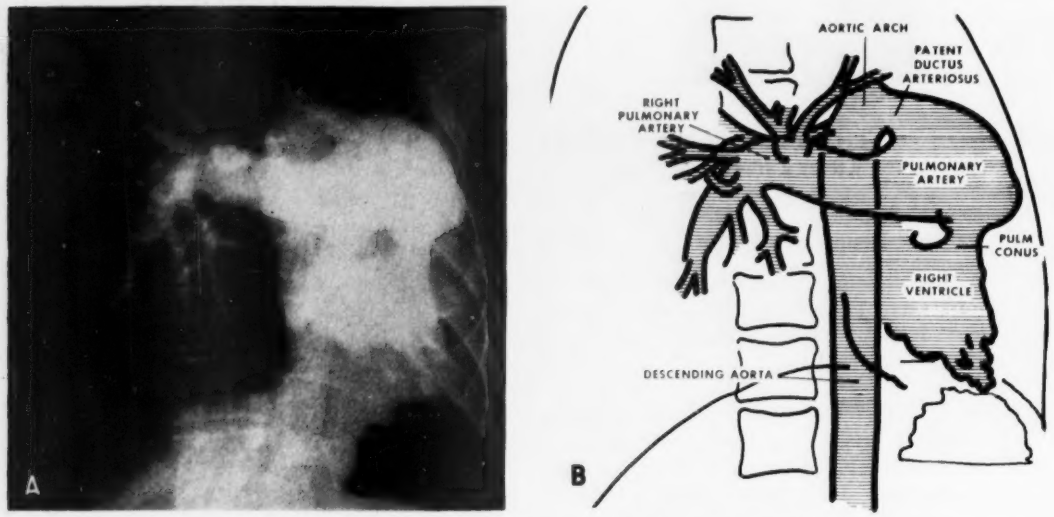

FIGURE 2. *Angiocardiogram Taken at Two Seconds in the Frontal Projection* (A). *A markedly dilated pulmonary artery fills the descending aorta through a large, short patent ductus arteriosus.* B = *tracing of* A.

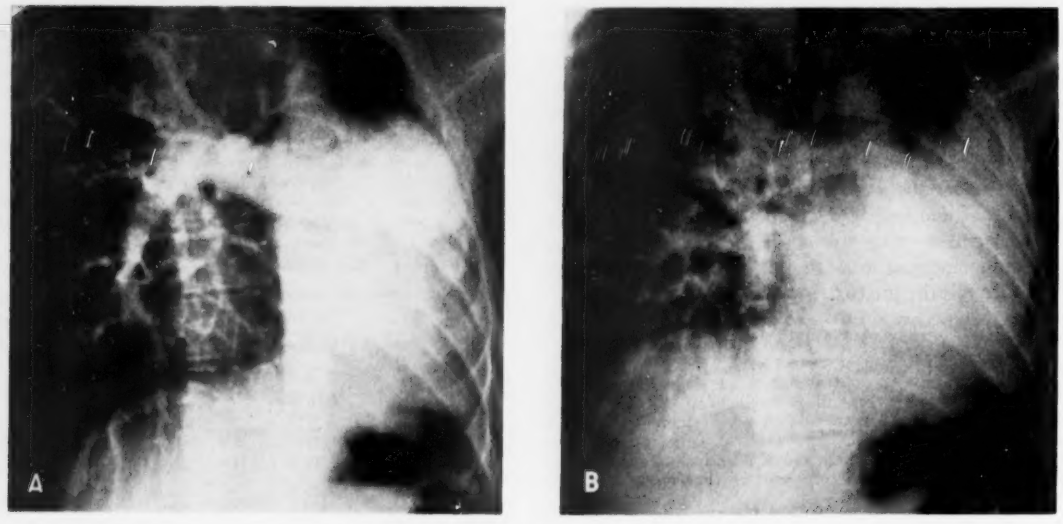

FIGURE 3. *Further Angiocardiographic Studies.*

Angiocardiogram at three seconds (A) *again reveals opacification of the ductus and the descending aorta. Pronounced dilatation of the pulmonary arterial tree and herniation of the right lung into the left upper portion of the chest are apparent. There is no left pulmonary artery. At eight and a half seconds* (B) *the ascending aorta is filled from the left ventricle in a normal manner. (In neither this film nor subsequent ones was the descending aorta seen again, presumably because the contrast material was diluted by blood shunted into the descending aorta through the ductus.)*

The significant data obtained by cardiac catheterization (Table 1) were severe pulmonary arterial hypertension, shunting of oxygenated blood into the pulmonary artery, normal oxyhemoglobin saturation of blood in the right brachial artery and distinctly reduced saturation of blood in the right femoral artery. These findings confirmed the bidirectional nature of the shunt through the ductus.

Discussion

The collected literature[1, 3, 5] indicates that congenital aplasia is three times more frequent in the left lung than in the right. It is more common in males than in females by a ratio of 3:2. Most patients with this lesion die in infancy or early childhood of either respiratory infection or the consequences of associated congenital anomalies. However, as might be anticipated from the clinical and physiologic experience with pneumonectomized patients,[6, 7] isolated unilateral pulmonary agenesis is compatible with a long, relatively unrestricted existence. In the reported cases 3 patients lived to fifty-eight, sixty-five and seventy-two years of age. Early diagnosis and prompt treatment of complicating respiratory infections may be expected to improve the longevity of patients with this condition.

The diagnosis should be considered when physical and roentgenographic examinations reveal marked displacement of the heart and mediastinal structures to either side of the thorax without evident cause, such as atelectasis or fibrothorax. The thorax on the affected side may be underdeveloped, as in the case reported here, but this is not a frequent finding. Demonstration of complete absence of bronchial and pulmonary vascular elements unilaterally by bronchography and angiocardiography establishes the diagnosis.

The observation of cyanosis and clubbing of the toes without similar changes in the fingers originally led to the diagnosis of patent ductus arteriosus with severe pulmonary hypertension and reversal of ductus flow.[8-10] This striking clinical phenomenon results from the fact that the point of insertion of the ductus is distal to the left subclavian artery. Unoxygenated blood transmitted through the ductus from the pulmonary artery is thus poured into the descending aorta and does not reach the brachiocephalic arteries in appreciable quantities. This situation was vividly demonstrated in the angiocardiogram and by the difference between the oxyhemoglobin saturations in the brachial and femoral arteries, the former being within the normal range. The absence of a typical ductus murmur in this patient can be ascribed to the altered relation in aorticopulmonary pressures.[10, 11]

Severe pulmonary arterial hypertension associated with patent ductus is usually the result of pulmonary arteriosclerosis, the pathogenesis of which is not entirely understood.[9, 10] A ductus of large diameter may transmit a left-right shunt of such magnitude as to exceed the normally large blood-flow capacity of the lungs and thereby produce moderate pulmonary hypertension. Currently, it is believed that persistence of the hypertension caused by a very large pulmonary blood flow leads to sclerosis of the small pulmonary arteries, which in turn aggravates the hypertension.[10] If this hypothesis is correct the tendency for pulmonary arteriosclerosis to develop was accentuated in the patient described above, since his ductus was large and his pulmonary vascular capacity only half normal. From the history of cyanosis of the toes for eight years it can be concluded that a grade of pulmonary arterial hypertension severe enough to cause partial reversal of ductus flow must have been of long standing.

Ligation of the ductus was considered. On the basis of previous poor results in patients with reversal of ductus flow,[12, 13] as well as the technical difficulties involved in ligation of a short, thick ductus, it was decided not to attempt surgical intervention.

Summary

The case of twenty-two-year-old man with congenital absence (agenesis) of the left lung and a patent ductus arteriosus is presented. Pulmonary arterial hypertension severe enough to cause reversal of flow through the ductus was present. This combination of congenital lesions was suspected clinically and confirmed by angiocardiography, bronchography and cardiac catheterization.

We are indebted to Dr. Claude E. Forkner for his encouragement and for permission to study the patient in this report.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39291

PRESENTATION OF CASE

A sixty-seven-year-old widow was admitted to the hospital because of fever, malaise and increasing drowsiness.

Twelve days before admission the patient "caught the virus" and had a temperature of 103°F. There were no localizing symptoms, except that about a week and again twenty-four hours before entry she had pain in the back radiating around the flanks. It was not definitely known how long this persisted, but she denied similar pain on admission. She also had some dysuria, with polyuria and nocturia, became drowsy and slept most of the time, but was easily awakened. She had little appetite for food; however, she drank large quantities of juices and water.

She denied having pain or any other symptoms referable to the gastrointestinal or genitourinary tract. Eight years before admission she was said to have had hypertension, but this was asymptomatic and nothing more was known about it. There was a suggestion in the history that she had had polydipsia for a long time; however, a diagnosis of diabetes had never been made.

Physical examination showed a well preserved woman who seemed sleepy but was easily aroused. The skin was of good color, but dehydration was marked. The neck veins were not distended. The heart and lungs were normal. The abdomen was lax and easily palpated. The aorta seemed to be wide and to have a prominent pulsation, especially in the epigastrium. The abdomen was otherwise normal. The femoral and popliteal pulses were palpable; the dorsalis-pedis pulse was absent. There were no other abnormal findings.

The temperature was 99°F., the pulse 120, and the respirations 18. The blood pressure was 110 systolic, 70 diastolic.

The urine was clear amber, had a pH of 5.0 and gave a + test for albumin, an orange-brown reaction for sugar, ++ tests for diacetic acid and acetone and a negative test for bile. The specimen was insufficient for specific-gravity determination. The sediment contained 3 to 6 white cells, no red cells and many fine granular casts per high-power field. Examination of the blood revealed a hemoglobin of 16.5 gm. per 100 cc. and a white-cell count of 48,000, with 93 per cent neutrophils and 6 per cent lymphocytes. The neutrophils contained toxic granules, and many were band forms. The hematocrit was 40 per cent. The nonprotein nitrogen was 32 mg., and the blood sugar 321 mg. per 100 cc.; the sodium was 120 milliequiv., the potassium 7.2 milliequiv., the chloride 89 milliequiv. and the carbon dioxide 28 milliequiv. per liter. A stool specimen was guaiac negative. An electrocardiogram demonstrated a normal rhythm at a rate of 100, a PR interval of 0.14 second, a QRS interval of 0.07 second and a normal axis. The P waves were notched in Leads 2, 3, aVR, aVL and aVF; the QRS segments were normal; the ST segments were depressed in Leads V_4, V_5 and V_6; the T waves were diphasic in Lead aVL (Fig. 1). A roentgenogram of the chest was normal except for elevation of the right side of the diaphragm; there was no air beneath the diaphragm. A plain film of the abdomen showed the stomach to be distended with gas. Gas was present in the small bowel and cecum, but there was no abnormal distention. On the right side of the abdomen was a conical density, with its base extending from the first to the fifth lumbar vertebra at the midline and its apex close to the right lateral abdominal wall (Fig. 2).

The patient was given an intravenous infusion and insulin according to the urine tests. On the second hospital day in the morning the temperature rose to 101°F., and she became cyanotic and vomited guaiac-negative material. The blood pressure was 80 systolic, 60 diastolic, the pulse 120, and the respirations 30. A lumbar puncture revealed clear spinal fluid under an initial pressure equivalent to 50 mm. and a final pressure equivalent to 38 mm. of water. Intravenous therapy and insulin were

continued as before. The hemoglobin was 12.5 gm. per 100 cc. There was now marked tenderness and spasm in the right upper quadrant and right costovertebral angle. The patient remained in the same condition until 4:30 a.m. the next day, when the blood pressure was found to be 75 systolic, 60 diastolic. An attempt to pass a Levin tube precipitated the vomiting of ++++ guaiac material. A short while later she became very restless and then collapsed within a few seconds. No peripheral pulse could be felt. Blood was given, but she died within a few minutes.

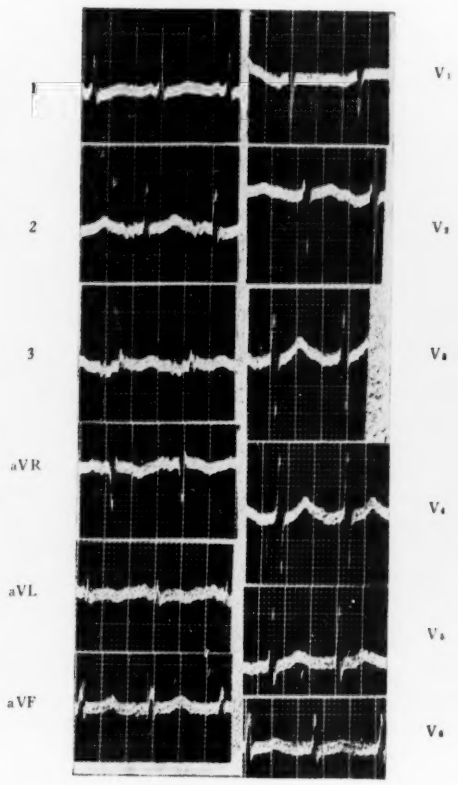

FIGURE 1.

Blood drawn 20 minutes before death was subsequently reported as follows: the blood sugar was 328 mg. and the nonprotein nitrogen 34 mg. per 100 cc., and the sodium 119 milliequiv., the chloride 87 milliequiv., the potassium 6.27 milliequiv. and the carbon dioxide 22 milliequiv. per liter; the hematocrit was 32 per cent.

DIFFERENTIAL DIAGNOSIS

DR. J. WALLACE ZELLER*: May I see the x-ray films?

DR. JOHN F. GIBBONS: The chest film is not remarkable. The stomach is distended with gas and there is gas in the duodenum, cecum, small bowel and rectum without evidence of distention. A somewhat conically shaped density, which is widest at the midline, is present on the right side of the abdomen and extends from the first to the fifth lumbar vertebra; its apex is almost at the right lateral abdominal wall (Fig. 2). This has obliterated the psoas-muscle shadow on that side; the left psoas-muscle shadow is faintly visible.

FIGURE 2. *Plain Film of the Abdomen. Arrows point to the margins of the mass.*

DR. ZELLER: Does the mass extend to the left?

DR. GIBBONS: The mass does not extend to the left of the midline. There is no calcification in the abdominal structures that I can see. I cannot make out the shadow of the right kidney, but the liver shadow appears to be well under the costal margin.

DR. ZELLER: Can you see the abdominal aorta? Is there any calcification that might indicate the abdominal aorta? (In the history the aorta was said to be wide and pulsating in the epigastrium.)

DR. GIBBONS: I can see no shadow that represents the lateral wall of the abdominal aorta. It is hidden by the large amount of gas and débris in the bowel.

*Associate physician, Massachusetts General Hospital.

DR. ZELLER: Is there anything about the films that suggests intestinal obstruction?

DR. GIBBONS: I should not suspect intestinal obstruction.

DR. ZELLER: Was the thoracic aorta normal?

DR. GIBBONS: The aorta is moderately tortuous and widened. There is no evidence of calcium in it.

DR. ZELLER: That is information; I do not know exactly what I can do with it.

The electrocardiograms were probably taken to obtain evidence of a possible myocardial infarction. I do not believe they provided a good basis for such a diagnosis. Even if they did, I believe I should be forced to consider other conditions of as great or greater importance in causing this patient's death. The failure to demonstrate air below the right leaf of the diaphragm indicated that it was not possible to demonstrate by this means an upper gastrointestinal perforation or subphrenic abscess with gas-producing organisms. There was no convincing evidence, at the initial examination at least, of upper gastrointestinal obstruction.

The history of polydipsia, the blood sugar levels and the urinary findings certainly justify the diagnosis of diabetes. This was not true diabetic coma, however, for the respirations were not described as hyperpneic and the carbon dioxide was in the range of normal. This rules out diabetic acidosis. The normal nonprotein nitrogen rules out renal insufficiency or uremia as the principal factor in the production of the clinical picture.

The patient was in a shock-like state even before there was definite evidence of gastrointestinal bleeding. Once this was observed, however, she collapsed and died. The occurrence of this bleeding automatically rules out, as a single diagnosis, some of the abdominal conditions mentioned above and also such additional ones as acute cholecystitis, acute pancreatitis and a ruptured appendix with abscess formation. The possibility of bleeding from a peptic ulcer, gastric carcinoma or gastritis must be seriously considered, and I cannot actually be certain that one of these conditions was not present. The fact that there was no clear-cut previous history of digestive disturbance does not favor any of these causes of bleeding but does not rule them out. Nor does the fact that the patient's nutrition was good at the time of entry — very good, I should judge from the chest films. I do not know how to explain the mass seen on x-ray examination in the right side of the abdomen by any of the diagnoses mentioned above unless it represented an abscess associated with previous perforation in an ulcer or carcinoma of the upper gastrointestinal tract. The development of tenderness and spasm in the right upper quadrant and right costovertebral angle on the second day was probably significant, and may have represented spread of such an infection. It is a fact to remember that massive hemorrhage and perforation can occasionally occur within a few days of each other in peptic ulcer.

In considering other causes for this patient's illness, vascular accidents involving abdominal viscera must be discussed. The possibility of arterial embolism or thrombosis or venous thrombosis involving mesenteric vessels might well account for many aspects of the clinical picture. The comment about the possibility of a wide, pulsating aorta in the epigastrium suggests the presence of a high abdominal fusiform aneurysm here, or possibly a widened aorta in association with a dissecting aneurysm. The fact that the femoral and popliteal pulses were palpable possibly weighs somewhat against the latter diagnosis on a statistical basis. Obliteration of the femoral pulses takes place, however, only when dissection involves the bifurcation of the aorta with subsequent obstruction of one or both femoral vessels. In some cases, this does not occur. A diagnosis of dissecting aneurysm seems to fit the entire clinical picture better than any other that I have considered.

I should like to go through the protocol again from the point of view of a diagnosis of dissecting aneurysm. Many of the findings that did not mean too much at first mean more when this diagnosis is considered. I think there must have been other facts in the history before admission that were not elicited. The first point is the site of the pain. A week before entry and again twenty-four hours before entry the patient had pain in the back radiating around the flanks. I am not told in what part of the back, the upper or lower, the pain was, but the fact that it radiated around the flanks makes me think that it was in the middle of the back. In that respect it was somewhat lower than the pain usually associated with dissecting aneurysm of the aorta. However, it is known that low-back pain may occur in some of these cases. Although this patient had a history of hypertension going back some years, she did not have an elevated blood pressure on admission. Most persons with dissecting aneurysm have such a history, but the hypertension persists for some time after the dissection. I believe the initial tear in the aorta probably took place a full week before admission, when she had the first pain. As her general condition worsened during the week, the blood pressure came down to the level found at admission. The fact that the aorta seemed to be wide and had prominent pulsations I believe I should accept even though it did not show up by x-ray examination. In most physical examinations one would not be too much impressed with that finding, but in this particular case I think it may have been significant. It is possible that what was felt was part of the mass that was present on the right side of the abdomen.

The high white-cell count does not fit in particularly well with the diagnosis of a dissecting aortic aneurysm alone. Usually, the white-cell count, although elevated, is not that high. In this patient there was a fair amount of dehydration, and certainly, if that mass in the abdomen was an area of hemorrhage resulting from final rupture of a dissecting aneurysm, a white-cell count that high would not be too unusual.

The development of marked tenderness and spasm in the right upper quadrant and right costovertebral angle indicates that some change in the abdominal situation occurred. I wonder whether at that time the aneurysm, in addition to having ruptured into the tissue about the right kidney, had dissected into the lumen of the bowel. The gastrointestinal bleeding may have occurred as the result of rupture or leaking of the aneurysm directly into the bowel lumen or slow oozing of blood from infarcted bowel supplied by an occluded mesenteric vessel. It is highly likely, however, that there had been some gastrointestinal bleeding before that time because a lowered blood pressure was previously noted. This, of course, could be explained by continued oozing into the large mass. The possibility that the abdominal mass was due to dissection of the right renal artery, with final rupture into the tissue about the right kidney, has to be considered quite seriously.

My final diagnoses are dissecting aneurysm of the abdominal aorta, with secondary dissection of the branches to the right kidney and the upper bowel and with final rupture and hemorrhage. The patient also had diabetes mellitus. Regarding the latter diagnosis, I toyed with the idea that some acute accident to the pancreas had occurred, producing sudden diabetes. I have never heard of such a sequence, and I do not want the suggestion to be taken too seriously. I believe this patient had diabetes that was tremendously aggravated by the terminal situation.

Dr. Gordon S. Donaldson: Was an amylase test done?

Dr. Winfield S. Morgan: No.

Dr. Zeller: When I read the record originally I felt somewhat hurt because of the scanty information provided. I jotted down additional data I wanted to learn. These were the serum amylase, results of blood cultures, whether the stool examined had been passed or whether it was a finger specimen, and whether any peristalsis had been heard.

Dr. Donaldson: I should like to ask Dr. Gibbons whether that shadow is consistent with a pancreatic cyst?

Dr. Gibbons: I think not; first of all, the shadow lies almost entirely to the right of the midline and does not seem to extend up along the left upper quadrant toward the tail of the pancreas, and, secondly, the stomach is not displaced even though it is greatly dilated with gas. I should expect a pancreatic mass of this size to displace the stomach.

Dr. F. Dennette Adams: Has not Dr. Zeller neglected the fever and the so-called virus infection that appeared at the start of this illness? Almost every patient who has a fever is currently said to have a "virus infection." One must be wary of accepting that diagnosis. In my opinion the fever and high leukocyte count at onset make it impossible to escape a diagnosis of some infection of intraperitoneal or abdominal viscera, with perhaps eventual abscess formation. Barring leukemia or bone-marrow metastatic disease, a leukocyte count of 48,000 is rare except in infection.

Dr. Morgan: I was about to ask you if you had seen a case of ruptured aneurysm with a white-cell count of 48,000.

Dr. Adams: Such a count would certainly lead me away from that diagnosis. The patient started with fever, and unless it could be established that she actually had a virus infection — some acute upper respiratory symptoms or perhaps an attack of nausea, vomiting and diarrhea — I think one has to connect the fever with the terminal disease. Local suppurative infection is implied by the white-cell count. What sort? I do not know—perhaps gall bladder, pancreas or kidney.

Dr. Zeller: Is it not possible for a white-cell count to be this high with massive bleeding?

Dr. Adams: I do not recall ever having seen it this high. I would settle for 20,000 plus or minus but not 48,000.

Dr. Morgan: We could not remember a case of ruptured aneurysm that had that high a white-cell count.

Dr. Allen G. Brailey: At the time the white-cell count was 48,000, the hemoglobin was 16 gm. per 100 cc. Apparently the patient had not bled massively then.

Dr. Zeller: I should have to agree with that. I was looking for ways of making the white-cell count seem artificially high, one being marked dehydration.

Dr. Morgan: On the day after she received fluid it was 43,000.

A Physician: Did you attach any significance to the low sodium and high potassium in the presence of a normal nonprotein nitrogen?

Dr. Zeller: I think this electrolyte picture is likely to occur in terminal states. That is how I had interpreted it in this case. Probable replacement of cellular potassium with sodium accompanied what was actually present, a relative alkalosis. I should like to hear from anyone regarding any other significance that can be placed on these electrolyte findings.

A Physician: It is of interest from the point of view of hemorrhage into the adrenal gland.

DR. ZELLER: I implied poor adrenal function in mentioning terminal states.

CLINICAL DIAGNOSES

Abdominal sepsis.
Upper gastrointestinal hemorrhage.
Diabetes mellitus.

DR. J. WALLACE ZELLER'S DIAGNOSES

Ruptured dissecting aneurysm of abdominal aorta.
Diabetes mellitus.

ANATOMICAL DIAGNOSIS

Ruptured mycotic aneurysm (salmonella) of abdominal aorta.

PATHOLOGICAL DISCUSSION

DR. MORGAN: This proved to be an extremely interesting case, and I believe Dr. Zeller came about as close to the diagnosis as we could expect from anyone. At autopsy there was 300 cc. of clear, serous fluid in the right pleural cavity. The lungs were moderately congested and somewhat edematous. The heart was normal except for slight coronary atherosclerosis.

The findings of chief interest were in the abdomen, where there was a large retroperitoneal hematoma extending from just below the level of the diaphragm into the pelvis. This was chiefly on the right side, very little on the left, and surrounded the right adrenal gland and kidney. At this point in the autopsy the origin of the hematoma was thought to be a ruptured arteriosclerotic aneurysm of the abdominal aorta. However, on further dissection, the abdominal aorta was found not to be dilated and contained no aneurysmal sac. When the aorta was opened a defect in the wall was found about 3 cm. below the level of the renal artery that led to a small subintimal cavity filled with purplish-red, soft hemorrhagic material that was thought to be older than the larger portion of the hematoma, which was dark red and seemed to be fairly recent. At the time the case was presented at our daily autopsy conference, we were not completely satisfied with either our explanation of the clinical aspects of the case or the autopsy findings. There was not much arteriosclerosis or dilatation in the abdominal aorta, but we could offer no better reason for the rupture. Another point that disturbed us was the white-cell count of 48,000, since none of us had encountered a leukocytosis of this level due to a hematoma. However, we reluctantly concluded that the defect in the aorta had probably resulted from a tearing of an intimal atherosclerotic plaque, with dissection and hemorrhage through the wall and necrosis of retroperitoneal tissue causing the leukocytosis.

It was only several days later that we had the answers to our questions. Blood cultures taken both before and after death were reported to have grown out salmonella, and the sections of the aorta through the tear revealed numerous clumps of bacteria. The subintimal cavity contained older hemorrhage and necrotic material scattered throughout which were many polymorphonuclear neutrophils and clumps of bacteria. There were also clumps of bacteria in the wall of the aorta at some distance from the tear. This, then, was a mycotic type of aneurysm, and the probable sequence of events was as follows: this woman had a salmonella infection for ten to twelve days, and a septicemia developed; bacteria localized in the aorta with resultant necrosis and eventual rupture and hemorrhage. Dr. Kunz, perhaps you will comment on the bacterial aspect of the case.

DR. LAWRENCE KUNZ: The organism isolated from the patient's blood was *Salmonella typhimurium*. One might have expected to find *Salmonella choleraesuis*, which is more frequently associated with such localized processes. It must be remembered, however, that although certain types of salmonella are associated with specific clinical entities, almost any one of them can run the gamut of disease from rather benign gastrointestinal enteritis to a typhoid-like syndrome.

DR. MORGAN: The bowel at autopsy was not abnormal in appearance, and there were no lesions on the valves of the heart and no suggestion of endocarditis, which is the usual initiating factor in the production of mycotic aneurysm.

DR. ZELLER: Did you explain the gastrointestinal bleeding?

DR. MORGAN: The stomach contained a large amount of coffee-grounds and watery material; the mucosa was congested, and there were petechial hemorrhages, but no definite ulceration was identified. I think the material there resulted from the congestion.

DR. ZELLER: I do not want to be argumentative, but is it not possible that the changes that you showed as the result of the salmonella infection occurred after the rupture of the aneurysm — that is, as the patient's condition deteriorated, the salmonella gradually established themselves in the aortic tear? I must admit that the high white-cell count is now more easily understood in the light of the focal complication of salmonella infection.

DR. MORGAN: I am not certain that we can date the actual rupture, nor am I certain that the complaint of pain in the back actually indicated the rupture. The hematoma did not have the character of a week's duration; I should say it was of one or two days' duration. On the other hand the patient did have an abdominal mass as demonstrated by x-ray examination on admission. In view of her illness of about twelve days' duration and the absence of much arteriosclerosis or any aneurysmal change, I believe we are on safe ground in considering this a true mycotic aneurysm.

DR. ZELLER: Do you think the shadow seen on x-ray examination was the mass?

DR. MORGAN: Yes.

A PHYSICIAN: What was the appearance of the right adrenal gland?

DR. MORGAN: It was lost in the hematoma.

CASE 39292

PRESENTATION OF CASE

A sixty-two-year-old housewife was admitted to the hospital with a history of intermittent hemoptysis for thirty years.

The first episode, at the age of thirty-two, occurred shortly after her first child was born, lasted two to three days and was not associated with other symptoms. Four years later there was a similar episode, and a diagnosis of tuberculosis was made, although tubercle bacilli were not identified. She was hospitalized in a sanatorium for eight months. At this time she was in her third pregnancy, which was interrupted because of the diagnosis. Thereafter she was free of symptoms until seven years before admission, when she again coughed up small amounts of blood for seven days. One year later, after another episode, bronchoscopic examination was performed, with negative results. Two years before admission there was another period of hemoptysis, productive of several cupfuls of blood. In the last two months she had had a cough productive of blood-streaked sputum almost daily, and she had remained in bed because of "asthma," wheezing respirations and a sore throat.

Seven years before admission she had a left radical mastectomy for cancer; however, the details of this operation were not known.

Physical examination revealed the scars of previous operations. The right lobe of the thyroid gland was enlarged to three times the normal size. Otherwise the examination was negative.

The temperature was 98.8°F., the pulse 85, and the respirations 20. The blood pressure was 180 systolic, 100 diastolic.

The urine was normal. Examination of the blood demonstrated a hemoglobin of 13 gm. per 100 cc. and a white-cell count of 7200, with 69 per cent neutrophils, 23 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils.

Roentgenograms of the chest showed a smoothly ovoid density, 5 cm. in greatest dimension, within the right upper lobe at about the midportion of the lobe inferiorly and somewhat medially (Fig. 1 and 2). There were discoid areas of atelectasis in the anterior segment. There was a question of pressure on the right-upper-lobe bronchus near its origin, as well as upon the proximal medial aspect of the right intermediate bronchus. Several small calcific densities were observed at the extreme right apex. The left lung was clear. The heart, aorta and diaphragm were not unusual.

On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTMAN*: May I ask one question? I thought I read that the only previous operation was a radical mastectomy seven years before admission and on the physical examination it is stated "scars of previous operations."

DR. BENJAMIN CASTLEMAN: She had a thyroidectomy for thyrotoxicosis, a hysterectomy and a fistula in ano excised.

DR. PITTMAN: They were irrelevant.

In summary the symptoms of this woman's illness go back thirty years to the beginning of the hemoptysis, and a diagnosis of tuberculosis was made on clinical grounds apparently without the finding of organisms. She was in good health until seven years before admission, when she began coughing up blood again and began bleeding more often; she bled six and two years before admission. Each of the reported hemorrhages from thirty to two years before admission consisted of a fresh flow that lasted a few days and then stopped. Two months before this admission, when she bled again, the bleeding was different; that is why I think there may have been something unusual.

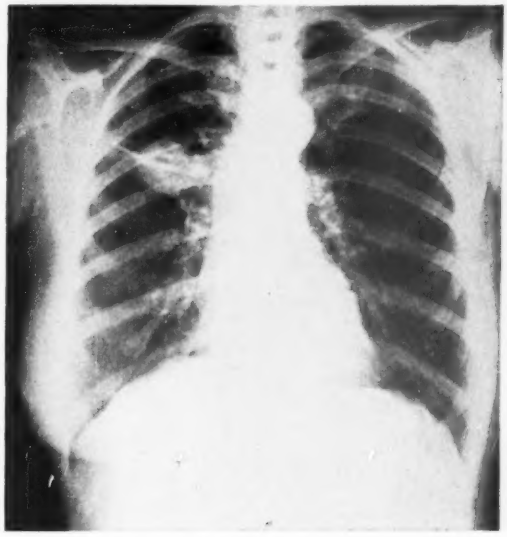

FIGURE 1.

May I look at the x-ray films, Dr. Wyman?

DR. STANLEY M. WYMAN: These films show a large, rounded mass in the right upper lobe (Fig. 1 and 2). We are fortunate in having old films taken seven years before the present admission that demonstrate the same shadow. This shadow has not changed much in seven years; it may be slightly

*Associate physician, Massachusetts General Hospital.

larger, but that is not too certain. Associated with it now is a great deal of atelectasis, which extends into the anterior segment of the right upper lobe. This mass is located centrally very close to the upper-lobe orifice, perhaps just below its main portion, and pressing upon it and the intermediate bronchus region. The lung fields otherwise are not unusual except for two or three small calcified scars.

DR. PITTMAN: The evidence for tuberculosis in the lung field is slight.

DR. WYMAN: There may be a few tiny scars, but I think they are inconsequential.

DR. PITTMAN: This woman had a benign lesion thirty years before admission that I think almost

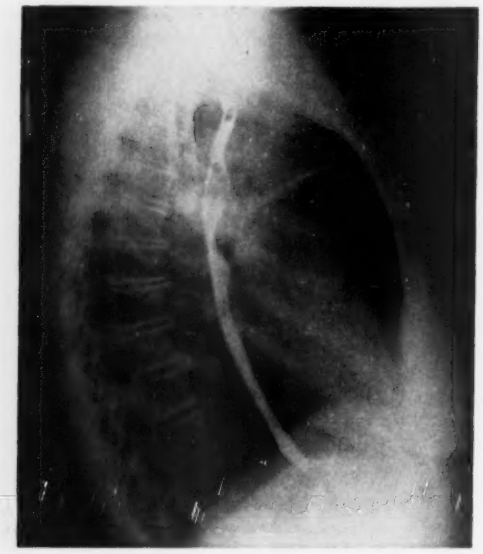

FIGURE 2.

surely was a bronchial adenoma, but I shall give a brief differential diagnosis before I come back to this.

There are three groups of lesions that should be considered. The first is infection, under which is tuberculosis, particularly a tuberculoma. I do not think she had a tuberculoma, and I am not going to discuss it any more. The second condition she could have had for thirty years is a congenital anomaly or arrest of some sort; of those the reasonable ones to consider are a bronchogenic cyst, a hamartoma or possibly an arteriovenous aneurysm or hemangioma. The cysts become infected, — she had no history of serious infection, — and they do not bleed extensively. Hamartomas in general do not have any connection with the bronchial tree, and this obviously had such a connection because it had bled over the years. The arteriovenous aneurysms or hemangiomas may bleed severely, but they are practically always associated with polycythemia, cyanosis, clubbing and a bruit over the lesion, which were not mentioned. I think these three possibilities can be discarded quite readily.

A bronchial adenoma may present mostly into the lumen of the bronchus, or it may be mostly in the lung parenchyma with very little extension in the lumen. The lesion was not seen at bronchoscopy six years before the present admission. I assume that the patient was bronchoscoped again shortly after this amount of history was obtained on admission to this hospital, and I think it is reasonable that the bronchoscopist's diagnosis was bronchial adenoma. However, the character of the bleeding had changed very definitely in the two months before admission; instead of episodic free bleeding she had daily streaking, which is the bleeding that is characteristic of bronchial cancer. We look upon adenomas as benign lesions, but occasionally cases have been reported in which there is malignant change in the adenoma. In these recent months wheezing respirations had also developed, — asthma is the way it was recorded, — indicating presumably partial bronchial obstruction; that was not mentioned before so I think something had been added in the bronchus. I suppose one has to mention endobronchial metastases, but as we see the lesion in this old film taken at the time the mastectomy was done I am going to discard that.

My diagnosis is adenoma of the bronchus largely within the lung and minimally within the bronchus; I think a carcinoma had arisen within the adenoma, producing the recent change in symptoms.

DR. CASTLEMAN: I gather that this patient was not bronchoscoped here. Dr. Sweet operated on her; perhaps he will comment on his reasons for not bronchoscoping her.

DR. RICHARD H. SWEET: The patient had been seen off and on for the six years since she had had the previous bronchoscopy in New Haven, where she was studied and correctly advised by the medical and surgical consultants. I proceeded to operate without a bronchoscopy because I believed that a bronchoscopy would not add much to the picture, would not change the indication for surgery and would not influence me about what I should do at operation. We went ahead and found what I thought was a typical adenoma. At operation she manifested her bleeding propensity very severely. Before we had the vessels of the lobe even dissected free, the anesthetist began to find a large amount of blood in his apparatus so that we had to clamp the bronchus before we had actually completed the dissection to stop her from aspirating blood. It was a very vascular, bloody tumor, as, of course, adenomas are.

DR. PITTMAN: That is why bronchoscopic biopsy of an adenoma is so dangerous.

DR. SWEET: That is a point that ought to be stressed. As a matter of fact when we bronchoscope these people we avoid biopsy if the growth looks

like an adenoma because it will bleed prodigiously from a bronchoscopic forceps punch biopsy.

Clinical Diagnosis

Bronchial adenoma.

Dr. Helen S. Pittman's Diagnosis

Bronchial adenoma, with carcinoma arising in it.

Anatomical Diagnosis

Bronchial adenoma, mucoepidermoid type, right upper lobe.

Pathological Discussion

Dr. Castleman: Dr. Sweet did a right upper lobectomy. In the posterior-branch bronchus was a large tumor, protruding into the bronchus like a finger (Fig. 3). The tumor had destroyed and penetrated the bronchus to form a large mass within the lung parenchyma. The gross cut surface did not look like that of the typical bronchial adenoma; it was white and slightly granular and contained many mucoid foci.

The histology of this tumor is interesting in that it corresponded to what has been called the mucoepidermoid type of adenoma. At first glance it appeared to be an infiltrating tumor with a great deal of stroma and looked like a straightforward squamous-cell carcinoma. The individual cells, however, were uniform; some showed slight keratinization, and there was a great deal of mucoid secretion. The infiltrative character of the tumor suggested a carcinoma, but many bronchial adenomas are infiltrating. I do not think we can say there had been any change to a true carcinoma. Liebow,[1] in his recent atlas on tumors of the lung, has described 2 such cases, in each of which the prognosis has been good. He confirmed the diagnosis in the case under discussion.

Dr. Pittman: I was impressed by the change in the type of bleeding and the apparently recent development of asthma; I suppose they coincided with the increase in the intrabronchial part of the adenoma.

Dr. Sweet: If my memory is correct, x-ray films were taken almost thirty years before admission and others off and on over the succeeding years, all of which showed this shadow. Of course in the early days no thoracic surgery was done for such things, but later physicians began to advise the patient to have the operation; it was only recently that she consented.

Dr. Castleman: I believe that very few adenomas become true carcinomas; they may infiltrate into the surrounding tissue, but I do not believe that the histology of the tumors changes sufficiently for one to consider them carcinomas.

Dr. Pittman: Benedict,[2] in his book, cited two references in which adenomas were reported actually to have changed to carcinomas. I did not read the references.

Dr. Castleman: I do not believe they do change; they may be low-grade carcinomas from the start.

Dr. Sweet: Did not Womack say that they do change?

Dr. Castleman: I believe Womack[3] who calls the bronchial adenoma a mixed tumor, considers most of them malignant.

Dr. Sweet: That belief has influenced surgeons extensively; we here are more or less in the minority in doing conservative operations on these patients. Many thoracic surgeons would do a pneumonectomy for a bronchial adenoma without any hesitation.

Figure 3.

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MEDICINE AND THE LETTER OF THE LAW

As a scholarly contribution to a better understanding of the role that the law has played in the development of modern medical practice, Spector's "Garrison Lecture"* of 1952 rates high. Going back even to the Code of Hammurabi, under which "If the physician make a severe wound with the bronze operating knife and the patient die . . . he shall have his hands cut off," he has been able to survey, in his own words, "certain areas of medical history in which the letter of the law fostered the growth of medicine."

*Spector, B. Fielding H. Garrison Lecture: growth of medicine and letter of law. *Bull. Hist. Med.* 26:499-525, 1952.

In another historical division, aside from that which Dr. Spector has traced, is the Persian *Zend-Avesta*, which established qualifications for surgical practice as well as a fee schedule. A surgeon, for example, was required to practice on three infidels before being allowed to operate on a true believer and, in regard to fees, "a priest he shall cure for a pious prayer, the head of a household for the price of a small draught animal, . . . the lord of a province he shall cure for the price of a four-span waggon." The Egyptians, even from the time of Imhotep, enforced rules of hygiene and sanitation and the Hebrews, announcing the appearance of diphtheria with a blast on the shophar, maintained strict rules of isolation in all cases of communicable disease.

So in various ways and in nearly all its fields medical practice, both private and public, has developed according to the law. It has developed, moreover, not through the arbitrary rules of dictators, but according to written law, for "under *written* laws the poor and rich an equal justice find."

In England distinctive regulations began to emerge during the early part of the reign of Henry VIII. Parliament then (1511-12) passed a law "that no person within the city of London nor within seven miles of the same shall take upon him to exercise and occupy as a physician or surgeon except he be first examined and approved by the Bishop of London or the Dean of St. Paul or the Bishop of the Diocese outside the city provided this Act be not prejudicial to the Universities of Oxford and Cantebrigge."

Largely through the influence of Thomas Linacre and others the Royal College of Physicians was chartered in 1518 to regulate the practice of medicine, a criminal code was enacted in 1532 that contained provisions regarding medical testimony in cases of violent death, and in the same year an Act of Parliament established commissioners of sewers throughout England.

To take a long step into the New World and into a later century one finds that in 1818 the General Court of Massachusetts passed an Act providing "that no person entering the practice of physic or surgery shall be entitled to the benefit of law,

for the recovery of any debt or fee accruing for his professional services unless he shall have been licensed by the officers of the Massachusetts Medical Society or shall have graduated a doctor in medicine in Harvard University." This is not to imply that any particular sanctity pertained to Harvard, but that Harvard had then the only school of medicine.

Dr. Spector points out that in general two legal methods are employed for the protection of the public. The restrictive method, employed mainly in the United States, establishes standards for medical practice and enjoins all those who do not qualify from engaging in practice. The definitive method, as followed in England, defines the legal qualifications for practice and permits the public to choose its practitioners. Woe betide the unqualified practitioner, however, for he is prosecuted "for claiming to be what he is not and for being a cheat and a fraud."

In such ways has the health of the people been always the concern of enlightened government.

REGARDING QUESTIONNAIRES

Holding no brief for those individuals and institutions that are addicted to questionnaires; believing, indeed, that the questionnaire represents a high point in the human capacity for being exasperating, the editors have nevertheless conducted a very brief poll of some two thirds of the subscribers to the *Journal*. In the implementation of this poll and at the risk of seeming cheerfully introspective, the management, thirsting for knowledge, sent a return postal card to 18,000 of those happy many who are privileged, for a trifling consideration, to receive the *Journal* at moderately regular intervals. The questions were simple, which probably explains the receipt of over 8300 replies, or 46 per cent of the total number distributed — as nearly as possible according to random selection. For the purpose of classifying the *Journal's* readers they were asked the type of work in which they indulged; in order that the editors might know how successfully the publication was filling the readers' requirements they were asked to check their choice among the three main features offered — original articles, reports on progress and the case records of the Massachusetts General Hospital — and the editorial section. As usual, the editors risked being caught in that deadly ambush in the path of progress that lies concealed behind the artless label "Suggestions."

Excluding for the moment the returns from Massachusetts, which seem to have followed a pattern of their own, Medical Progress led the ballot with 1813 votes, original articles and case records running practically neck and neck with 1663 and 1636 votes respectively. Conscious no doubt of the Biblical allusion to prophets in their own land, Massachusetts gave 1075 votes to original articles, 976 to Medical Progress, and 601 to the Case Records. The total figures are: Medical Progress 2789, original articles 2738 and Case Records 2237. Even the editorial section received 609 ballots.

A number of the suggestions were pertinent, were repeated by many of those replying to the questionnaire, and will be acted on if feasible and as the occasions arise. Leading suggestions were that more be published on medical economics, that there be more articles for the general practitioner, more pediatric case records and a section for abstracts from other journals.

Dividing the subscribers into types of practice or other activities it appears that internal medicine, including dermatology and syphilology heads the list with 2352 devotees; surgery, including the surgical specialties, comes next with 1954 and general practice third with 1751. Of the medical specialties, pediatrics claimed 319 and psychiatry and neurology 217. The remainder were scattered among such more definite specialties as anesthesiology, administration, industrial medicine, pathology, physical medicine, public health, radiology, and teaching and research.

PREVENTIVE MEDICINE

Elsewhere in this issue of the *Journal* one of the staff members of the Institute of Laboratories of the Massachusetts Department of Public Health has traced the developments in the production of the biologic preparations used in the treatment and prevention of diphtheria. Those who would like to learn the comparative merits of the products that they have been using over the years will now find that the task is fairly easy. Those who have

been somewhat unhappy on being told that a particular product was no longer obtainable will know that there was a good reason why.

These laboratories have supplied the products that, in the hands of the physicians of Massachusetts, have reduced the cases of diphtheria in the State from 9293 in 1901 to 23 in 1952, and the deaths in the same years from 1166 to 1. If the next generation of physicians will keep up the good work of utilizing the products for active immunization to the fullest extent, diphtheria will permanently have lost its sting.

One inevitable accompaniment of this low incidence of the disease is that a new generation of physicians is growing up who will never have seen a case of diphtheria. Some of them may thus fail to recognize an occasional case until it is too late for diphtheria antitoxin to prevent damage and even death. Just how to keep the level of suspicion high is a pressing problem.

Medical Miscellany. — *Dr. Alexander Mayer, of Paris, announces a great discovery — heating boilers, cooking, &c., by means of friction, instead of fuel. — Dr. Peasley's case of shoulder-joint operation is to be had in a pamphlet.*

Boston M. & S. J. *July 20, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

EAGAN — Edward F. Eagan, M.D., of Lynn, died on June 13. He was in his forty-eighth year.

Dr. Eagan received his degree from Yale University School of Medicine in 1930. He was associate chief of the ear, eye, nose and throat clinic at Lynn Hospital, and on the staff of Union Hospital in Lynn.

He is survived by his widow, his mother, two sons and three daughters.

LAHEY — Frank H. Lahey, M. D., of Boston, died on June 27. He was in his seventy-fourth year.

Dr. Lahey received his degree from Harvard Medical School in 1904. He was founder and director of surgery of the Lahey Clinic and surgeon-in-chief, Deaconess Hospital and the New England Baptist Hospital. He was a former president of the American Medical Association and also of the Interstate Postgraduate Medical Association, governor of the American College of Surgeons, and member of the American Surgical Association, the Southern Surgical Association, the New England Surgical Society, the American Urological Association, the American Gastro-Enterological Association and the Association for the Study of Internal Secretions.

Dr. Lahey is survived by his widow.

O'KEEFE — James V. O'Keefe, M.D., of Lynn, died on June 12. He was in his seventy-first year.

Dr. O'Keefe received his degree from Harvard Medical School in 1909.

He is survived by his widow, two sisters and a brother.

OLIVER — E. Lawrence Oliver, M.D., died on June 12. He was in his seventy-eighth year.

Dr. Oliver received his degree from Harvard Medical School in 1904. He was chief of the Department of Dermatology, Massachusetts General Hospital, and clinical professor of dermatology and syphilis, emeritus, at Harvard Medical School. He was a staff consultant for the Boston City Hospital, the Children's Hospital, the Boston Lying-in Hospital, the Massachusetts Eye and Ear Infirmary, the Faulkner Hospital and the Cable Memorial Hospital, Ipswich. He was a member of the American Dermatological Association and a fellow of the American Medical Association.

He is survived by his widow, a stepson, a stepdaughter, a sister and two brothers.

PALFREY — Francis W. Palfrey, M.D., of Boston, died on June 11. He was in his seventy-seventh year.

Dr. Palfrey received his degree from Harvard Medical School in 1902. He was assistant professor of medicine at Harvard Medical School, and chief of the Second Medical Service, Boston City Hospital. He was a fellow of the American Medical Association.

He is survived by his widow, two sons, a daughter, a grandchild and a sister.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

THE USE OF BIOLOGIC PRODUCTS IN THE CONTROL AND TREATMENT OF DIPHTHERIA IN MASSACHUSETTS

The present low incidence of diphtheria in Massachusetts, as revealed by the 1952 report of the Department of Public Health, Division of Communicable Diseases, showing only 21 cases and 1 death during the year, seems to call for some comment. One must regret that the members of the old State Board of Health could not witness what they earnestly worked for. In the year 1888, the Board recommended to the Legislature the establishment of a state vaccine laboratory to make smallpox vaccine. Biologic products for the control and treatment of diphtheria were then unknown. At that time, however, diphtheria was a disease to be gravely reckoned with, for during that particular year 1831 deaths from this cause were reported. Indeed, only twelve years previously, in 1876, the highest diphtheria death rate in the records of Massachusetts occurred — 195.82 per 100,000, or 3294 deaths. It is not with any idea of relaxing effort, but rather of learning, if possible, from the past accomplishments, that this phase of disease control in the State is reviewed.

The Massachusetts records on scarlet fever may be cited as the example of a disease without ade-

quate prophylactic immunization. The death rate for scarlet fever exceeded that of diphtheria for twenty-five of the years from 1842 to 1900. From the time that both diseases were made reportable and until the advent of prophylactic diphtheria immunizing agents, the numbers of reported cases were comparable (Fig. 1). Although in recent years low virulence and later the sulfonamides and antibiotics have greatly lowered the death rate of scarlet fever, nothing has happened to change the incidence of that disease.

Diphtheria Antitoxin

In 1894, the State Board of Health undertook the production of diphtheria antitoxin, and distribution was begun in March, 1895. Deaths attributed to

Figure 1. *Reported Cases of Scarlet Fever and Diphtheria, 1900–1950.*

diphtheria in the year 1894 totaled 1801. Never again in this state has that figure been reached. Unfamiliarity with the disease because of its low incidence in recent years has undoubtedly deferred early administration of antitoxin in many cases. The effect of the wide use of antibiotics on the throat cultures is well known, and may make laboratory diagnosis difficult. Antitoxin is now used almost entirely for treatment. The use of prophylactic antitoxin in 1000-unit doses has now almost ceased.

There has been little basic change in diphtheria antitoxin itself since it was first used. It is still produced in horses. Both concentration and purification have somewhat reduced the number of reactions, which were due to horse-serum sensitivity in the patient. Modifications of the methods of processing have eliminated pyrogenic reactions entirely.

Diphtheria Toxin-Antitoxin

Dr. Theobald Smith, the first director of the Antitoxin and Vaccine Laboratory (1895-1914) is credited with having first made and employed diphtheria toxin-antitoxin as an immunizing agent. Its use in guinea pigs was reported by Dr. Smith[1] in 1908. Dr. William H. Park, in New York City, began the toxin-antitoxin immunization of children. Massachusetts soon followed, and the Laboratory made and distributed the material from 1918 to 1947. Distribution was widespread until the early 30's. The downward trend in cases that began in 1923 has continued almost unchecked since that time. A slackening in the diphtheria immunization program, together with post-war importation of diphtheria, offers a possible explanation for the ominous rise in cases and deaths in the late 40's.

This biologic product had many staunch adherents among the medical profession who demanded it after the toxoid became available and even after distribution of toxin-antitoxin was discontinued. Reactions in the older age groups were few and less likely to be troublesome. There were several good reasons, however, for its being discontinued. Among these were the ease with which the toxin could be dissociated from the antitoxin by freezing, thus making the product toxic; the horse-serum content, which undoubtedly sensitized many; and its low antigenicity.

Schick Test

Few states have made more use of the Schick test than Massachusetts from its initial distribution in 1915 up to the present. This was particularly true of the first twenty years of this period, distribution later being limited to the high-school age groups. In 1923, Dr. Béla Schick, then of Austria, while on a tour of this country, visited the Laboratory. His visit and the resultant publicity gave new impetus to the use of the test. It would be very interesting but difficult to evaluate the contribution to diphtheria control made by this test. It focused attention on immunity, or the lack of it, on a "herd" basis. Population groups could be compared, city, rural and semirural. To many it must have been the first introduction to the "needle." In this manner and in other ways it had educational value. Besides evaluating antigens, the test itself is slightly antigenic, most noticeably as a small recall or "booster" dose to previously acquired immunity of below Schick level. Earlier beliefs regarding absolute specificity of immunity as indicated by negative Schick tests have given way to present concepts of decreased susceptibility with no guarantee of protection against mild diphtheria.[2] On the other hand, nurses who would formerly have been classed as susceptible (circulating antitoxin below the Schick level) have been reported as in constant attendance upon diphtheria patients without contracting the disease or having an appreciable rise in blood antibody titer.[3] Its value in today's population as a diagnostic tool to determine a person's susceptibility must be small indeed. Certainly,

Schick-negative persons, regardless of age, who are in contact with cases of diphtheria, even if they have been previously immunized, should receive a recall injection of diphtheria toxoid, *provided* that they are not highly sensitive to the protein itself. The blood antitoxin level of the average Schick-negative adult in Massachusetts today is surely much lower than that in 1920.

In 1920 many of the persons with Schick-positive reactions had had some immunity stimulus from contact with the larger number of persons who were carriers of the causative organism, even though they remained Schick positive.

Schick-test materials have been improved since the procedure was first used. At first the toxin and diluent were distributed separately, with the attendant danger of mistakes. The use of peptone, and later human albumin, as a stabilizing agent allowed the test material to be distributed as ready for use. The toxin has been highly purified, a procedure that has resulted in a higher degree of stability. Also, the "heated toxin control" has been supplanted by a dilute purified toxoid, which accurately predicts the subject's ability to receive a larger immunizing dose of toxoid (Moloney test). As a matter of fact, this control test is more antigenic than the Schick toxin. Thus, because of this ability both to predict reactions to immunization and to immunize, the control test has become the most important part of the Schick-testing procedure.

Fluid Diphtheria Toxoid

Distribution of crude fluid toxoid began in 1932. Work was started in the middle 30's toward improving the mediums in which the parent toxin was produced. By 1938 a peptone-free medium had begun to go into production lots. The resulting toxoid had higher antigenicity and less reactivity. Since 1949 it has been possible to separate off fractions that contain most of the materials causing reaction, and the toxoid has been distributed in a purified form. This work has brought beneficial results to immunization not only in Massachusetts but also throughout the country in products from other laboratories. Foreign countries, able to provide themselves with the basic materials, have also shown eagerness to use the medium.

Although no attempt is made here to document all the work referred to, a chronology of diphtheria-toxoid development without mention of the work of Pappenheimer[4] and Robinson,[5] of these laboratories, and Mueller,[6] of Harvard Medical School, would be inexcusable. The wide acceptance of this work, both in this country and abroad, is indicative of its merit.

Multiple Precipitated Antigens

In the account, thus far, of the biologic products used for the control of diphtheria in Massachusetts, it has been assumed that 90 per cent or more of those used in the State were furnished by the State Biologic Laboratories. Since these products are furnished free to the physicians and boards of health of Massachusetts, this is probably a safe assumption, except for the early use of multiple precipitated antigens. The state laboratories were delayed in beginning the distribution of these products, although studies dating back to 1941 and before were reported on alum-precipitated diphtheria toxoid. During the 1946–1947 increase in diphtheria in the State (Fig. 1), when laboratory supplies of fluid toxoid were quite low, a small amount of precipitated material was purchased by the Department. Supplies produced covered the needs, but the precipitated antigen was distributed, although this took some salesmanship in the beginning.

Before the Laboratories began the preparation of precipitated antigens now being distributed — namely, diphtheria and tetanus toxoids, combined, aluminum phosphate precipitated (DT), and diphtheria and tetanus toxoids and pertussis vaccine combined, aluminum, phosphate precipitated (DTP) — a small survey was made to determine, if possible, the future demand. When general distribution of the two products began, distribution figures soon showed that the survey had given no indication of the great demand. Some indication of the wide use of the new products was the low distribution of fluid diphtheria toxoid, which, in 1948, had dropped below even the previous World War II years. This downward trend continued until distribution was stopped in 1951 as a civil-defense measure to encourage the use of DT, with the attendant immunity to tetanus.

These trends indicate that, at least by 1942, small but increasing amounts of fluid toxoid were being replaced by other products in this state. Since the school programs still used fluid toxoid exclusively during that time this change was presumably due to the fact that physicians in private practice purchased precipitated antigens for immunizing preschool children.

The distribution of DT and DTP, which began in 1950, has increased at a rapid rate up to the present. It seems evident that for the past year most of the children of the State in the age group between three months and one year were getting their basic diphtheria immunization by the use of DTP. Enough DTP was distributed during 1952 to give basic immunization (3 injections of 0.5 cc. each) to 120,000 children — adequate for the total annual births in the State. It is also known that considerable commercial material was used during the same period.

Discussion

The low antigenicity of toxin-antitoxin was mentioned above. Laboratory tests on animals rank

diphtheria antigens as follows: the precipitated toxoids, fluid toxoids and toxin-antitoxin in that order, with TA a poor third. The Schick conversion rate in man is another method and has been commonly used to assay various diphtheria preparations, although there may be great variation in the immunizability[7] of various populations. A Schick conversion rate of 93 to 96 per cent found four months after TA immunization in 1921 in Boston would require allowance for the high Schick conversion rate of the nonimmunized in such an area. Children tested in Boston's crowded North End in 1923 were reported only 15 per cent Schick positive, whereas during the same period in outlying districts of Boston, they were found to be 72 per cent Schick positive.[8] It is also of interest that workers at that time estimated that for each case of diphtheria diagnosed there might be as many as 5 undiagnosed cases. The age of two to three years was then considered to be the age of greatest susceptibility as deduced by Schick testing. Although the literature places TA in last place on the basis of the Schick conversion rate, the immunizability of the population at the time of its use was high enough to give it a higher value than it deserved.

Massachusetts is in a favorable position so far as control of diphtheria is concerned. As Figure 1 indicates, this position was attained by means of a weapon believed to be weak, toxin-antitoxin, in addition to aid given by natural infection. Fluid toxoid was distributed and used in time to increase the advantage gained. It was not until the advent of toxoid that the case rate in Massachusetts dropped below the national average. The most powerful weapon available — precipitated toxoid — came into use too late, it is believed, to deserve much credit for the present low incidence of diphtheria in Massachusetts.

Although earlier precipitated antigens were likely to cause reactions, including "antigenic cysts," they are being increasingly employed. It is doubtful if much fluid diphtheria toxoid is used at present. In the precipitated products in use today, containing purified toxoid and less aluminum than formerly, reactions are much less of a problem. The future may determine whether diphtheria control requires as high a toxoid content in multiple antigens as is now believed to be needed. Although reactions to the diphtheria-toxoid protein in young children are infrequent, they do occur. If these reactions could be reduced still further in number and severity, without detectable increase in susceptibility, even more progress would have been attained. An increasing tendency to use DTP up to the age of ten makes the diphtheria-toxoid content of this product important. Lowering the diphtheria toxoid content of DT would be of even more importance from the standpoint of reactions.

Another aspect of the problem, however, is important: each ten-year period finds the highest incidence in an older age group. Workers abroad have reported outbreaks of diphtheria in populations reported as having fair to good immunization histories.[2, 3, 9] A question to be answered is, How much will the admittedly better immunity imparted by the multiple precipitated antigens compensate for the present low immunizability of the adult population? Although one hopes that extensive epidemics would not occur in such a population and that any diphtheria occurring would not be severe, until more is known it seems logical for adults without toxoid sensitivity to be given a booster dose every five to ten years. The problem of how to get adults to present themselves for immunization without the immediate threat of disease will be a hard one to solve. If the incidence of the disease ever increases to its former level, adults should be encouraged in every way possible to be immunized.

Considerable interest is now being taken in the preparation of a product, either singly or combined with other antigens, that can be used safely in adults.[10] Clinical trials have indicated that 1 Lf (flocculating unit) of diphtheria toxoid may be safely administered to young adults in the armed forces without previous Moloney testing. Reactions to a dose of this size have not been severe even in toxoid-sensitive persons.

James A. McComb, D.V.M.
Assistant Director-in-Charge
Biologic Laboratories, Institute of Laboratories

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BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Dr. Howe and the Forsyth Infirmary. By Rollo Walter Brown. 8°, cloth, 188 pp. Cambridge: Harvard University Press, 1952. $3.50.

Mr. Brown has written the history of the Forsyth Dental Infirmary for Children, located in Boston, and of its director, Dr. Percy R. Howe, who began his work in 1928. The four Forsyth brothers, of Boston, endowed the Infirmary, which enjoys an international reputation. Dr. Howe was greatly interested in a biologic basis for chemistry and its relation to modern medicine. During his directorship, interns came from all over the world to study and to engage in research. He strongly influenced the development of dental medicine and took part in the reorganization of the Harvard Dental School. He wrote a great many articles; a bibliography of 14 pages is appended to the text. The small book is well published and should be in every collection on the history of dentistry.

The Prenatal Origin of Behavior. By Davenport Hooker, Ph.D., Sc.D., professor of anatomy and chairman, Department of Anatomy, University of Pittsburgh School of Medicine. 8°, cloth, 143 pp., with 6 illustrations and 4 tables. Lawrence, Kansas: University of Kansas Press, 1952. $2.50. (*Porter Lectures*, Series 18.)

This monograph is based on the Porter Lectures of the School of Medicine of the University of Kansas. The three lectures comprise: fetal activity in infrahuman vertebrates; the sequence in human fetal activity; and the significance of structural and functional interrelations in prenatal activity. The literature on the subject has been reviewed, and there is a bibliography of fourteen pages. There are indexes of authors and subjects; the small book is well published.

Commotio Cerebri: Cerebral concussion and the postconcussion syndrome in their medical and legal aspects. By Cyril B. Courville, M.D., director, Ramon Cajal Laboratory of Neuropathology, Los Angeles County Hospital, Los Angeles. 4°, paper, 161 pp., with 12 illustrations. Los Angeles: San Lucas Press, 1953. $5.25.

This monograph on concussion discusses the condition in all its aspects, beginning with history and including the cerebral circulation, pathology, clinical syndromes and management of the postconcussion state. The pertinent literature is evaluated, and there is a bibliography of 19 pages as well as an index; the publishing is good. The book should be in all neurologic and psychiatric collections.

You and Tuberculosis. By James E. Perkins, M.D., managing director, National Tuberculosis Association; and Floyd M. Feldmann, M.D., assistant to the managing director, National Tuberculosis Association. With the collaboration of Ruth Carson. 12°, paper, 176 pp. New York: Alfred A. Knopf, 1952. $2.50.

This small book by two well known authorities is intended primarily for patients and their families. The material is well organized, and the text well written in a narrative style.

The Principles of Neurological Surgery. By Loyal Davis, M.S., M.D., Ph.D., D.Sc., (Hon.), professor of surgery and chairman, Division of Surgery, Northwestern University Medical School, Chicago. Fourth edition. 8°, cloth, 544 pp., with 354 illustrations and 5 plates. Philadelphia: Lea and Febiger, 1953. $8.50.

This new edition of a standard work has been thoroughly revised, and many important additions have been made to the text. The material on peripheral-nerve surgery has been entirely revised and rewritten to include findings made from the study of several hundred cases resulting from injuries received during World War II. There is a good index, and the publishing is excellent. The book should be in all collections on surgery of the nervous system.

Emergencies in Medical Practice. Edited by C. Allan Birch, M.D., F.R.C.P., physician, Chase Farm Hospital, Enfield. Third edition. 8°, cloth, 587 pp., with 143 illustrations. Edinburgh: E. & S. Livingstone, Ltd., 1952. $7.00. (Distributed by Williams and Wilkins, Baltimore.)

The first edition of this English book was published in 1948, and this new edition has been revised and brought up to date. Twenty-two specialists contributed to the work, and the various contributions are signed. There is a good index, and the publishing is excellent. The printing was done in Great Britain.

NONCLINICAL NOTES

PASSANO FOUNDATION AWARD

John F. Enders, Ph.D., associate professor of bacteriology at Harvard Medical School, was awarded in June the ninth annual Passano Foundation Award for his success in developing methods for culturing poliomyelitis viruses in tissue.

Dr. Enders is an associate fellow of the Massachusetts Medical Society.

NOTICES

POSTGRADUATE COURSES CONDUCTED BY ARMY MEDICAL SERVICE

The Office of the Surgeon General, Department of the Army, has announced that a series of 10 short postgraduate courses will be conducted by the Army Medical Service during the fiscal year 1953-54.

The courses, which are listed according to the hospital or installation where they will be given are as follows: Brooke Army Medical Center, Clinical Laboratory Course (March 15-19, 1954): Fitzsimons Army Hospital, Symposium on Pulmonary Diseases (September 21-25, 1953). Clinical Electrocardiography and Recent Advances in Cardiovascular Diseases (November 9-14, 1953): Letterman Army Hospital, Rehabilitation Techniques in Neuromuscular Diseases and Disabilities (April 5-10, 1954): Armed Forces Institute of Pathology, Forensic Pathology (November 2-6, 1953) and Pathology of the Oral Regions (March 8-12, 1954): and Walter Reed Army Medical Center, Seminar in Urology (September 7-9, 1953). Symposium on Circulation and Homeostasis (October 5-9, 1953). Symposium on Physical and Mental Health Standards (April 16-17, 1954) and Recent Advances in Medicine and Surgery. Including Psychosomatic Aspects of Medicine and Surgery (April 19-20, 1954).

Applications for admission to any course must be submitted at least six weeks before the opening date. Army medical officers on active duty and full-time Civil Service physicians at Army installations should forward their applications through channels to the Office of the Surgeon General, Department of the Army, Washington 25, D.C. (attention: Personnel Division).

AMERICAN INSTITUTE OF DENTAL MEDICINE

The tenth annual meeting of the American Institute of Dental Medicine, will be held at the Desert Inn and El Mirador, Palm Springs, California, October 25 through 29. Details of the program may be obtained from Miss Marion G. Lewis, executive secretary, 2240 Channing Way, Berkeley 4, California.

FOURTH CONGRESS OF PAN AMERICAN MEDICAL WOMEN'S ALLIANCE

The fourth congress of the Pan American Medical Women's Alliance will be held at the Beekman Towers Hotel, First Avenue and Forty-Ninth Street, New York City, September 24 through October 1. In addition to a scientific program of general interest, there will be round-table luncheon discussions with leaders speaking Spanish and English. Through the sponsorship of leading New York medical women those interested in a special field will have opportunities to attend clinics of their choice. The Medical Women's Association of New York will conduct tours of the New York Hospital-Cornell Medical Center and Columbia-Presbyterian Medical Center, a boat trip around Manhattan Island, tour and luncheon at the United Nations, visits to Radio City and the Empire State Building and a drive to Hyde Park.

(*Notices concluded on page xn*)

Some questions about filter cigarettes that may have occurred to you, Doctor

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A: The drop in skin temperature occurring at the finger tip induced by filtered cigarette smoke was measured according to well-established procedures. (a, b)

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References Cited

a. *J.A.M.A.*, Vol. 103, 1934, p. 318
b. *J.A.M.A.*, Vol. 135, 1947, p. 417

* PATENT APPLIED FOR

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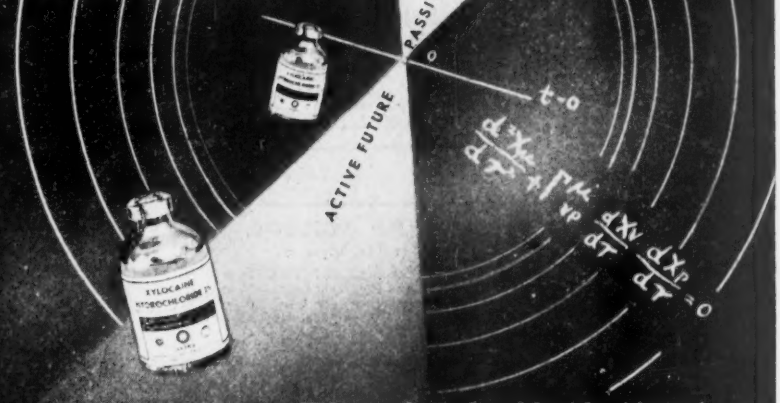

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NOTICES (*Concluded from page 124*)

SOCIETY MEETINGS AND CONFERENCES

JULY 23–25. West Virginia State Medical Association. Page 44, issue of July 2.

AUGUST 10–16. Institute on Teaching and Improving Esophageal Speech. Page 44, issue of July 2.

AUGUST 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

SEPTEMBER 24–OCTOBER 1. Fourth Congress of Pan American Medical Women's Alliance. Page 124.

OCTOBER 4–9. American Academy of Pediatrics. Page 1126, issue of June 25.

OCTOBER 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 25–29. American Institute of Dental Medicine. Page 124.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETY

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SEPTEMBER 23.
NOVEMBER 18.
JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 23

THURSDAY, JULY 23

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
9:00–10:00 a.m. Grand Rounds, Russell Room, House of the Good Samaritan.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
11:00 a.m.–12:00 m. Pediatric Conference. Mt. Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JULY 24

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JULY 25

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JULY 27

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 28

9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JULY 29

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

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